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PERINEURIAL CYSTS OF THE SPINAL NERVE ROOTS

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During the course of dissection of the filum terminale at autopsy in about 30 adults 5 cases of cysts (neither parasitic nor dermoid) on the extradural portions of the posterior sacral or coccygeal nerve roots were encountered. Since but 2 reports of similar cysts have come to my attention, this experience seems worth recording, particularly since it was possible to determine the site of origin of the cysts in these cases.

Marburg [1] described 4 cases of cysts of the spinal ganglia. The cysts were solitary in 3 cases and multiple in the fourth. Hinrichs [2] recorded a case in which 3 cysts occurred on the posterior thoracic and lumbar roots, in the region of junction of the root and the ganglion. The subjects were between 61 and 77 years of age and presented no symptoms referable to the cysts. Marburg concluded that it was likely that the cysts followed old hemorrhage into the ganglia. The exact site of origin of the cysts was not determined in the cases reported.

REPORT OF STUDY

The subjects in the present series were between 49 and 63 years of age and, so far as is known, presented no symptoms or signs referable to the cysts. The cysts occurred on the second, third, fourth or fifth sacral or the coccygeal nerve roots. They presented on the posterior roots in the region of passage through the dura mater. The posterior root or the ganglion or both the root and the ganglion were involved. The anterior roots were compressed by the larger cysts at a given level, the compression occurring near the junction of the anterior and the posterior root. A few cysts were observed on the nerve roots of the extradural portion of the filum terminale. All cysts were therefore intraspinal and essentially extradural.

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1. Marburg, O.: Zur Pathologie der Spinalganglien, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **8**:103, 1902.

2. Hinrichs, U.: Intraradiculäre Cysten an Spinalganglien, Virchows Arch. f. path. Anat. **287**:242, 1932.

The cysts varied from one the size of a pinhead to one measuring 2 cm. in diameter and involving the entire ganglion (fig. 1). The fluid of the cyst was either clear and colorless or faintly yellowish. The cavity of the cyst appeared to be entirely closed. In 1 case injection of colored solution into the cyst resulted in its passage into the subarachnoid space. However, one could not be certain that the communication was not artificial and produced by the pressure of injection rather than preformed. Similar injections in other cases did not result in the escape of fluid into the meningeal spaces or elsewhere around the cyst.

One of the cysts was multiloculated, a flattened bundle of nerve fibers forming a partition between the two main portions of the cyst

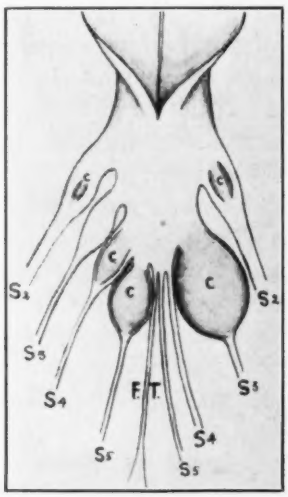

Fig. 1.—Drawing to show the approximate position and transition in size of various cysts (*C*) of the sacral nerve roots.

(fig. 2*B*). In all cases, the thin wall of the cyst was continuous externally with the arachnoid and dura mater covering the posterior root. A few small blood vessels were sometimes seen along the wall of the cyst. The smaller cysts usually appeared on the posterior aspect of the dorsal root or its ganglion.

Microscopic study of cysts of various sizes in serial sections after embedding in paraffin or pyroxylin showed clearly their relationships. The early stage in cyst formation was that of a space between the arachnoid which covers the root, or the perineurium, and the outer layer of the pial cover of the root, or the endoneurium (fig. 3). This usually began in one portion of the circumference of the perineurial space, the larger cysts compressing the nerve root to one side (fig. 3*E*, *c*). Some of the cysts, however, surrounded the entire circumference of the nerve root, which lay within the center of the cyst

(fig. 4 *A, d*). The cyst occasionally dissected through the nerve root and was entirely surrounded by nerve fibers or ganglion cells (fig. 4 *A, y*). In such a case a single section would lead one to believe that the cyst arose from within the center of the root or ganglion (fig. 5). However, study of serial sections demonstrated the direct continuity of the central intraneural or intraganglionic portion of the cyst and the portion which lay clearly within the perineurial space. The early stage in the formation of these cysts was therefore that of a space between the endoneurium and the perineurium. All stages of transition up to the large cysts occupying the entire diameter of the nerve root or those occurring within the center of the nerve root were observed.

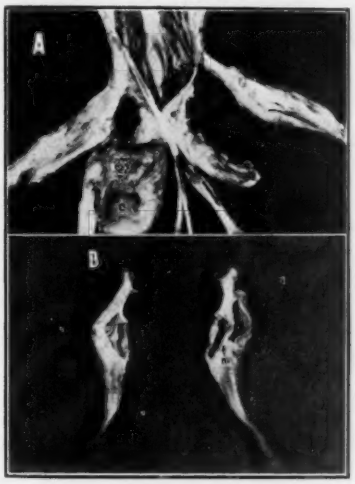

Fig. 2.—Photographs of (*A*) a cyst (*c*) on a lower sacral nerve root and (*B*) a cyst on a posterior sacral nerve root. Note the division of the cyst into two compartments by a partition of nerve fibers in the center (*n*).

The wall of the cyst at its surface consisted of one or several layers of flattened arachnoid or perineurial cells with a delicate connective tissue framework, surrounded by the fibrous tissue of the dura (epineurium), which was usually much thinned. The inner, or neural, border of the cyst was formed of flattened endothelium and reticulin of the endoneurium. Thickening of the connective tissue wall frequently occurred. The endoneurium ensheathing the individual nerve fibers, it will be recalled, is derived from the inner layer of the pial sheath.[3] The outer layer of the pial sheath forms the endoneurial sheath surrounding the nerve bundle. The inner wall of the cyst may, therefore, be represented by the peripheral extension of the outer or, if this is

3. Tarlov, I. M.: Structure of the Nerve Root: I. Nature of the Junction Between the Central and the Peripheral Nervous System, Arch. Neurol. & Psychiat. **37**:555 (March) 1937.

ruptured, of the inner layer of the pia mater (endoneurium). The epineural-perineurial (outer) wall of the cyst was, usually, very vascular, often presenting thin-walled blood vessels immediately under the lining membrane. Large blood vessels were sometimes encountered within the nerve bundle adjacent to the cyst (fig. 3 *A, b*). Groups of cuboid cells resembling those of the arachnoid were frequently observed

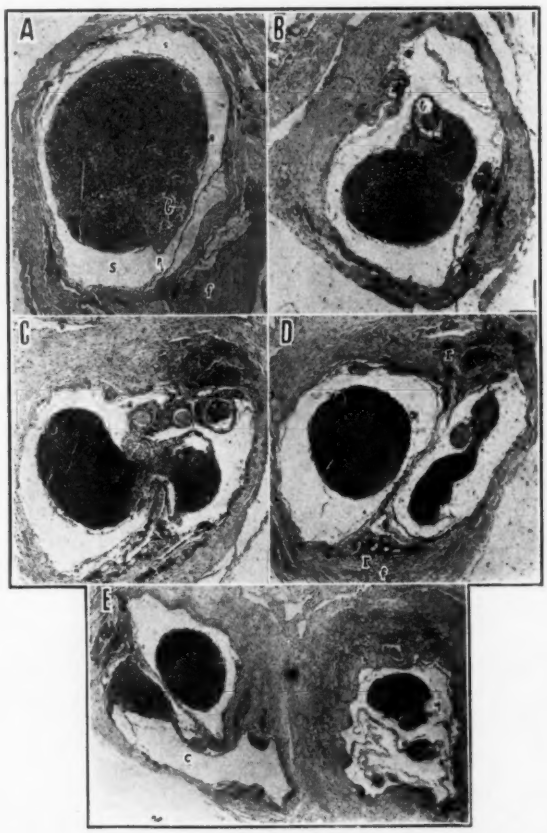

Fig. 3.—*A*, cyst beginning in the perineurial space (*s*) between the endoneurium (*e*) and the perineurium (*p*). The epineurium (*f*) surrounds the perineurium. Note the large, thin-walled blood vessel (*b*) just under the endoneurium. × 35.

B, increase in size of the cyst shown in *A*. × 28.

C, bifurcation of a bundle of nerve fibers, with beginning of formation of two cysts. Note the prominence of blood vessels adjacent to the cysts. × 28.

D, double cyst of a nerve root. Note the round cell infiltrations (*r* and *r'*) in the epineurium (*f*). Infiltration may involve the perineurium. × 28.

E, increase in size of a cyst (*c*). A bundle of nerve fibers is compressed at one side. There is early cyst formation (*y*) on an adjacent root. × 28.

in the wall of the cyst, and whorl formations with psammoma bodies were not uncommon. On one occasion loose myxomatous tissue was observed within the cyst, but otherwise the cavity consisted of a fluid-filled space; occasionally trabeculae of reticulin, with elongated or stellate cells, coursed through the cyst.

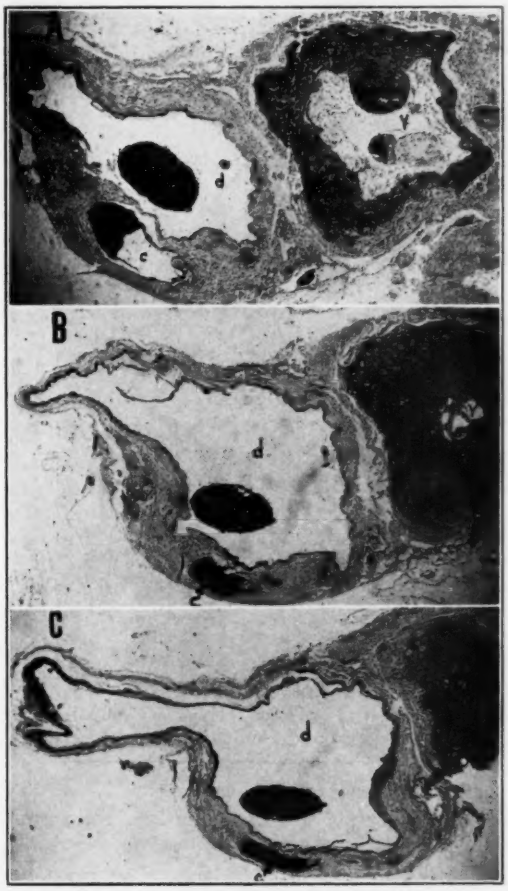

Fig. 4.—*A*, increase in size of cyst *d* and decrease in that of cyst *c*. Cyst *y*, shown in figure 3 *E*, has extended within the nerve root and ganglion. × 19.
B, increase in size of cyst *d* and decrease in size of cysts *c* and *y*. × 15.
C, increase in size of cyst *d* and disappearance of the other two cysts. × 15.

In instances in which nerve fibers or ganglion cells surrounded the cyst, either entirely or in part, evidence of degenerative changes was present. Disintegration of myelin sheaths and nerve fibers was seen in Weigert-Pal and Gros-Bielschowsky preparations, and cresyl violet stains revealed chromatolysis of ganglion cells. Accumulations of

phagocytes filled with fat or blood pigment occurred, and mucicarmine revealed a few droplets of mucin within large round cells. There was dropping out of nerve cells in the corresponding ganglion, with proliferation of fibroblasts and formation of connective tissue scars.

Diffuse round cell infiltration or foci of lymphocytes and plasma cells were encountered in some of the specimens (fig. 3 *D*). They were observed in the connective tissue sheaths of the filum and actually within the nerve roots or ganglia. Such inflammatory cells occurred in the walls of or at some distance from the cyst, involving nerve roots on which cysts did not occur.

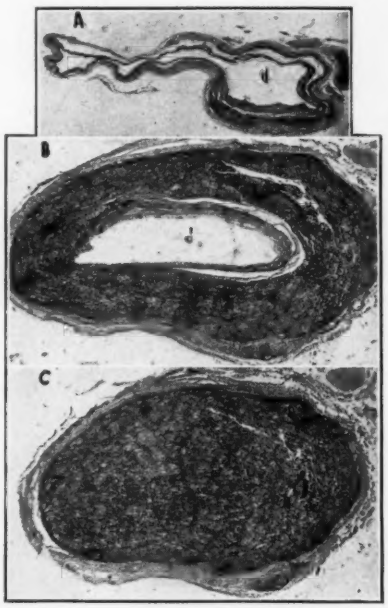

Fig. 5.—*A*, further increase in size of cyst *d*. × 7.

B, decrease in size of cyst *d* and extension into the posterior root ganglion. × 12.5.

C, disappearance of cyst more distally along the ganglion. × 12.5.

Sections shown in figures 3, 4 and 5 are taken from a collection of serial sections through a specimen of multiple cysts on the sacral nerve roots. All sections were stained with hematoxylin and eosin.

Early cyst formation was observed on some of the smaller nerve roots which course through the extradural portion of the filum terminale (filum terminale externum). They occurred on the nerve roots adjacent to the prominent vein which marks approximately the middle of the filum. These nerve roots belong to the coccygeal segments of the spinal cord.

COMMENT

It seems clear that the cysts develop in the space between the endoneurial and the perineurial sheath (perineurial space). The occurrence of round cell infiltration around the cyst raises the question of an inflammatory origin. The extent of this infiltration in at least 1 case in which serial sections were studied was greater than one would expect as a result of damage to the surrounding tissue from pressure of the cyst. Moreover, inflammatory cells occurred within the connective tissue of the extradural portion of the filum terminale at some distance from the cyst. The absence of striking inflammatory signs in some of the cases is not necessarily against an inflammatory basis, since the process may have occurred sometime previously, most of the inflammatory cells having disappeared in the interim. Positive evidence is therefore more significant than negative evidence in this respect. It is likely that an inflammatory process may have resulted in sealing off of a portion of the perineurial space—perineuritis and epineuritis followed by enloculation of fluid. There may have been further increase in size of the cyst as a result of transudation from the thin-walled blood vessels bordering it. This condition may be analogous to adhesive spinal arachnoiditis (circumscribed serous spinal meningitis) with formation of the so-called arachnoid cysts. It is of interest, however, in this connection that no striking evidence of such meningeal change occurred in these cases.

In 1 case a small amount of myxomatous tissue occupied the interior of the cyst, but there was no evidence of massive mucinous degeneration. Formation of fluid as a result of degeneration within the walls of the cyst is unlikely, particularly in view of the absence of degenerative changes in the wall of the cyst in other cases. The endothelial cells lining the cyst are of an extremely flattened type, and it is unlikely that such cells could be responsible for production of the fluid in the cyst. Chemical analysis of the fluid would be of interest in this connection.

The reason for the apparent predilection of these cysts for the sacral nerve roots is not clear. However, this region seems prone to various pathologic alterations. The cases described by Marburg and Hinrichs are similar to those reported here, and the cysts in their cases occurred in the thoracic and lumbar regions. Complete dissections of all cerebrospinal nerve roots were not made in all cases of the present series, but this should be done in the future.

Although the cysts appeared to be without clinical significance in these cases, one wonders whether they may not be responsible for the discomfort in certain cases of sciatica or nerve root pains in which any other pathologic basis has been excluded. This awaits further studies with clinical and pathologic correlations.

The question arises as to whether these cysts bear any relation to the rare extradural spinal cysts (10 cases of which have been recorded)

described by Schlesinger;[4] Krause;[5] Mixter;[6] Elsberg, Dyke and Brewer;[7] Lehman,[8] and Cloward.[9] The cysts in the cases reported were monolocular or multilocular and single or multiple occurring in the thoracic or in 1 case in the lumbar region. Most of the cysts occurred in young persons, the youngest being 12 and the oldest 46. In most cases the cyst was filled with a clear, colorless fluid, its walls consisting of fibrous tissue with a lining of flattened endothelial cells. The description of the cysts, therefore, suggests a histologic similarity to those of the present series. Elsberg, Dyke and Brewer suggested a possible origin of the cyst from a congenital diverticulum of the dura mater or a herniation of the arachnoid through a congenital defect in the dura. The cyst in 1 of the cases reported by Lehman and in all those described by Elsberg, Dyke and Brewer was attached to the dura near the exit of a posterior root. Is it possible, therefore, that some of these cysts represent advanced stages of the perineurial cysts described, the cyst extending posteriorly through the dura and its pedicle later becoming obliterated? One cannot answer this question definitely, but in the future particular attention should be paid to the relation of such cysts to the posterior root and its ganglion.

Although perineurial cysts seem to be few, their rarity is probably attributable somewhat to the neglect with which the lower end of the spinal cord and the nerve roots and ganglia are treated in autopsies done as a routine.

SUMMARY

Cysts of the extradural portion of the posterior spinal nerve roots develop within the perineurial space. They are often multiple, and in the cases recorded here they involved the sacral and coccygeal roots. It is likely that they may develop as a result of inflammation in the sheaths of the nerve roots followed by enloculation of fluid in the perineurial space. Increase in size of the cyst probably is a result of transudation from its many thin-walled blood vessels. The smaller cysts which occur along the coccygeal nerve roots may be considered as true cysts of the extradural portion of the filum terminale. However, it must be remembered that they develop within the perineurial space of these small nerve roots as they course through the connective tissue structure of the filum. The clinical significance of these cysts remains to be determined.

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7. Elsberg, C.; Dyke, C., and Brewer, E.: The Symptoms and Diagnosis of Extradural Cysts, Bull. Neurol. Inst. New York **3**:359, 1934.

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HISTOLOGIC CHANGES IN SENILE DEMENTIA AND RELATED CONDITIONS

STUDIED BY SILVER IMPREGNATION AND MICROINCINERATION

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The histopathologic diagnosis of the senile psychoses with dementia is based mainly on the silver stains. The major points of differential diagnosis, clinical and pathologic, are summarized in a table (table 1) based on the data contained in the literature, as well as on our own experience. The literature has recently been reviewed by Grünthal,[1] von Braunmühl [2] and Alexander.[3] Though the senile plaques appear to be rather specific for the senile dementias, especially those of the Alzheimer group, neurofibrillar changes, most of them of slightly dissimilar morphologic character but of similar staining properties (hyperargyrophilia), as in the senile neurofibrillar changes of Alzheimer type, have been observed in other diseases of the central nervous system, such as dementia paralytica (Bielschowsky and Brodmann [4]), chronic epidemic encephalitis (Hallervorden [5]), paralysis agitans (Lewy [6]),

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1. Grünthal, E.: Die pathologische Anatomie der senilen Demenz und der Alzheimer'schen Krankheit (mit besonderer Berücksichtigung der Beziehungen zur Klinik), in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, vol. 11, 1930, pp. 638-672.

2. von Braunmühl, A.: Pick'sche Krankheit, in Bumke, O.: Handbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 11, pp. 715-873.

3. Alexander, L.: The Neurofibrils in Systemic Disease and in Supravital Experiments, with Remarks on Pseudo-Atrophy of the Brain, Arch. Neurol. & Psychiat. **32**:933 (Nov.) 1934.

4. Bielschowsky, M., and Brodmann, K.: Zur feineren Histologie und Histopathologie der Grosshirnrinde mit besonderer Berücksichtigung der progressiven Paralyse, J. f. Psychol. u. Neurol. **5**:173, 1905.

5. Hallervorden, J.: Zur Pathogenese des postencephalitischen Parkinsonismus, Klin. Wchnschr. **12**:692, 1933.

6. Lewy, F. H.: Die Lehre von Tonus und der Bewegung, in Alzheimer, A., and Lewandowsky, M.: Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie, Berlin, Julius Springer, 1923, no. 34.

TABLE 1.—*Differential Diagnosis of Senile and Presenile Psychoses with Dementia (Senile Dementias)*

	Senile Dementia	Focal Senile Dementia, Alzheimer Type (Alzheimer's Disease)	Focal Senile Dementia, Pick Type (Pick's Disease)
Clinical symptoms	Change of personality, with loss of memory and mental abilities, alteration of libido; insidious onset; in severe forms amnestic-delirious syndrome	Mild or severe focal symptoms: aphasia, apraxia, agnosia; in Pick's disease sometimes cortical blindness; loss of memory and mental abilities	
		Overactivity: paraphasic talkativeness, occupational hyperactivity	Deep akinesia and stupor; rapid loss of motor speech, only unarticulated sounds being made; rigidity, motor negativism, stereotypies
Age group	Over 55	Over 45	Over 45 (most of the patients older than in Alzheimer group)
Gross pathologic changes	Diffuse atrophy	Diffuse and focal cortical atrophy	Focal cortical and subcortical atrophy with only slight diffuse atrophy; predilection for frontal, central and first three temporal convolutions; atrophy usually more severe than that in Alzheimer's disease; the central white matter and the basal ganglia on one or both sides atrophic
Microscopic pathologic changes	Diffuse cellular loss; moderately numerous senile plaques; rare and few fibrillary changes; no typical Alzheimer strands; no vascular changes, unless due to coincidental arteriosclerosis	Slight diffuse cellular loss; fibrillary changes of Alzheimer type; numerous senile plaques; cortical architecture not fundamentally altered; white matter and basal ganglia unaffected; no vascular changes, unless coincidental	Severe alteration of cortical architecture, third layer best preserved; severe gliosis with demyelination of white matter, cellular loss and gliosis of basal ganglia; remaining cortical and subcortical ganglion cells showing shrinkage or swelling, with thickening or net formation of intracellular neurofibrils; in some swollen cells argyrophilic balls (granulovacuolated cell disease); no fibrillary strands or whorls of Alzheimer type; only a few (or moderately numerous) senile plaques; thickening (fibrosis and hyalinization) of walls of capillary and supracapillary intracerebral blood vessels

spastic spinal paralysis (Barrett[7] and Schaffer[8]), amyotrophic lateral sclerosis (van Bogaert and Bertrand[9]), rabies (Achúcarro[10]) and pellagral ganglion cell disease (Parhon and Papinian,[11] Valtorta[12] and

7. Barrett, A. M.: A Case of Alzheimer's disease with Unusual Neurological Disturbances, J. Nerv. & Ment. Dis. **40**:361, 1913.

8. Schaffer, K.: Zur Pathologie und pathologischen Histologie der spastischen Heredodegeneration (hereditäre spastische Spinalparalyse), Deutsche Ztschr. f. Nervenh. **73**:101, 1922.

9. van Bogaert, L., and Bertrand, I.: Pathologic Changes of Senile Type in Charcot's Disease, Arch. Neurol. & Psychiat. **16**:263 (Sept.) 1926.

10. Achúcarro, N.: Zur Kenntnis der pathologischen Histologie des Zentralnervensystems bei Tollwut, in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1909, vol. 3, p. 143.

11. Parhon, R., and Papinian, J.: Note sur les altérations des neurofibrilles dans la pellagre, Compt. rend. Soc. de biol. **58**:360, 1905.

12. Valtorta, D.: Sulle alterazioni delle cellule nervose corticali in un caso di tifo pellagroso, Riv. pellagrol. ital. **8**:58 and 74, 1908.

Rezza [13]); in systemic diseases associated with cachexia and dehydration or edema, notably, cholera asiatica (Chanutina,[14] Michailow [15] and Alexander [3]), dysentery and intestinal tuberculosis (Alexander and Wu [16]), uremia (Lafora [17] and Hechst [18]) and cachexia thyreoparathyreopriva (Balli,[19] Lewy [6] and Rasdolsky [20]); in death from starvation and exposure to cold (Donaggio [21]), and in hibernation (Tello [22]).

A somewhat similar, but not identical, change could be produced experimentally by soaking fresh human brain tissue in water or solutions of sodium chloride before fixation (Alexander [3]). Common to all these changes is hyperargyrophilia. Concerning the histochemical nature of this hyperargyrophilia only hypotheses were available until microincineration revealed that the hyperargyrophilic neurofibrillar strands of Alzheimer's ganglion cell disease are characterized by ample deposits of heat-resistant mineral ash, which is absent from normal intracellular neurofibrils (Alexander and Myerson [23]). Most of these ash deposits were found to be calcium oxide. It seemed of interest, therefore, to investigate the question whether similar neurofibrillar alterations, notably, those occurring in Pick's disease and pellagral ganglion cell disease and those observed in edema and dehydration (pseudoatrophy)

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14. Chanutina, M. D.: The Question of Changes of the Spinal Cord in Cholera, Russk. Vratch **8**:1140; 1176, 1909.

15. Michailow, S.: Pathologisch-anatomische Untersuchungen der feineren Struktur der Gehirnrinde, der Rinde des Kleinhirns, des verlängerten und des Rückenmarks des Menschen bei asiatischer Cholera, Arch. f. Psychiat. **51**:587, 1913.

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18. Hechst, B.: Ueber Gehirnbefunde bei urämischen Zuständen, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:544, 1932.

19. Balli, R.: Lesioni del reticolo neurofibrillare endocellulare in mammiferi adulti totalmente o parzialmente privati dell'apparecchio tiro-paratiroideo e loro rapporto colla temperatura, Riv. sper. di freniat. **32**:803, 1906.

20. Rasdolsky, J.: Histologische Veränderungen in dem zentralen und peripherischen Nervensystem der Tiere mit exstirpierten Schild- und Nebenschilddrüsen, Ztschr. f. d. ges. Neurol. u. Psychiat. **106**:96, 1926.

21. Donaggio, A.: Effetti dell'azione combinata del digiuno e del freddo sui centri nervosi di mammiferi adulti, Riv. sper. di freniat. **32**:373, 1906.

22. Tello, F.: Las neurofibrillas en los vertebrados inferiores, Trab. d. lab. de invest. biol. Univ. de Madrid **3**:113, 1904.

23. Alexander, L., and Myerson, A.: The Mineral Content of Various Cerebral Lesions as Demonstrated by the Microincineration Method, Am. J. Path. **13**:405, 1937.

of the brain in systemic diseases associated with cachexia (the "soaking change," Alexander [3]) are characterized by a similar alteration in the ash picture. The scope of this investigation has been widened to include the senile plaques and certain observations concerning the special histopathologic changes in Pick's focal senile atrophy.

MATERIAL AND METHODS

This study is based on 18 human brains. In all cases blocks from area 10, the central region, areas 17, 18 and 19, the cornu ammonis and the area entorhinalis (in a few cases also from area 37, the island of Reil, the striatum and the thalamus opticus) were fixed in a 10 per cent solution of formaldehyde U. S. P., and frozen sections from these regions were stained with Bielschowsky's method of silver impregnation for intracellular neurofibrils. Neighboring blocks were fixed in 95 per cent alcohol and examined by Nissl's method and in some cases also with Masson's trichrome method and with hematoxylin and eosin. In some of the brains showing neurofibrillar alterations and in some of the normal brains, sections from blocks fixed in 95 per cent alcohol were examined by the microincineration method (Policard,[24] Scott [25] and Alexander and Myerson [23]). The microincinerations were carried out at the research laboratory of the Boston State Hospital. Part of the microscopic and photomicrographic work was completed at the neuropathologic laboratory of the neurologic unit of the Boston City Hospital.

Our data are presented in the form of a table (table 2), which includes the age of the patients, the time of autopsy after death, the main clinical, pathologic and neurohistologic data and the differential ratio of skull capacity to brain volume, expressed as the percentage of the skull capacity, as an indicator of atrophy or edema of the brain. A differential ratio below 4 per cent expressed edema, and one above 9 per cent, atrophy of the brain. The significance of this and other physicochemical data (specific weight, water content, water-binding capacity and the p_H) is discussed in a separate paper,[26] which was based on studies carried out in the same cases.

Detailed histologic protocols are given in only 4 representative cases, including 1 case each of Pick's disease, Alzheimer's disease and pellagral ganglion cell disease associated with chronic alcoholism with psychosis and 1 case of "water change" or "soaking change" observed in the severely edematous brain of a woman who had committed suicide by hanging.

REPORT OF CASES

CASE 6.—*Pick's disease (focal cerebral atrophy, type Pick).*

Clinical Note.—A woman aged 72 with senile dementia (Pick's disease) was confused, disoriented and amnesic. She presented stereotypies, giggled and laughed constantly, fixed her hair constantly and repeatedly blinked her eyes.

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24. Policard, A.: Sur une méthode de microincinération applicable aux recherches histochimiques, Bull. Soc. chim. de France **33**:1551, 1923.

25. Scott, G. H.: The Localization of Mineral Salts in Cells of Some Mammalian Tissues by Microincineration, Am. J. Anat. **53**:243, 1933.

26. Alexander, L., and Looney, J. M.: Physicochemical Properties of the Brain, Especially in Senile Dementia and Cerebral Edema: Differential Ratio of Skull Capacity to Volume, Specific Weight, Water Content, Water-Binding Capacity and p_H of the Brain, Arch. Neurol. & Psychiat. **40**:877 (Nov.) 1938.

Autopsy.—There was extreme atrophy of the cortical convolutions of both frontal and temporal lobes. The extremely atrophic parts were of harder consistency and slightly darker than less atrophic areas. The causes of death were: carcinoma of the left breast, with metastases to the lungs, and terminal bronchopneumonia.

Microscopic Examination.—Nissl and Masson Preparations: In the most severely diseased areas, most markedly in area 10 of both frontal lobes, the cortex was extremely atrophic, and the convolutions were narrow and reduced to pointed, bizarrely shaped ridges, which left widely gaping sulci between them (fig. 1 *B*). However, the cortical ribbon had nowhere disappeared and was of about the same, though greatly reduced, width all over the atrophic convolutions. The central white matter and the centers of the convolutional white matter in this region showed intense demyelination, in many places of the status marmoratus type, the areas of demyelination consisting of many small spheroid areas. The U-fibers were well preserved. In many of the convolutions, toward their pointed tips the U-fibers came so close to each other that they appeared in these places to make up the entire convolutional white matter. The central and convolutional white matter showed intense gliosis, made up of fibrillary and protoplasmic astrocytes and of oligodendroglia cells (fig. 2). This gliosis was so intense that in Nissl preparations of this region the convolutional white matter appeared darker and more densely cellular than the gray matter (fig. 1 *A*). In the fifth and sixth cortical layers almost all ganglion cells had disappeared and were replaced by moderately dense gliosis. The fourth layer was preserved in some places; in others it was replaced by irregular gliosis. The only layer which was consistently preserved, although greatly depleted of ganglion cells, was the third (fig. 1 *A*). Almost all its cells, however, showed severe pathologic changes: some showed extreme shrinkage (fig. 3 *A*), and others were swollen, giving the appearance of typical "Pick cells" (figs. 4 *A* and 5 *A* and *B*). There was moderately dense gliosis in this layer. The second layer was almost entirely depleted of ganglion cells. This, however, showed only very loose, slight gliosis; therefore, the second layer in these areas appeared to be part of a broadened lamina zonalis (fig. 1 *A*), which here also showed moderate astrocytic gliosis. In some places the diseased cortex showed the formation of a fine-meshed status spongiosus in its deeper layers (only in single instances in the superficial layers) but no foci of softening, either complete or incomplete. Many of the middle-sized and small blood vessels in the cortex and in the white matter showed thickening and hyalinization of all walls (fig. 6), but there was no instance of occlusion. In the cortical gray matter the capillaries showed thickening and hyalinization of their walls (fig. 7). In the area entorhinalis, which was one of the severely affected areas, the relatively best preserved layers were the laminae principales externae, beta and gamma, and the lamina dissecans. Sommer's sector of the cornu ammonis was entirely depleted of ganglion cells; however, there was only slight, loose gliosis replacing this defect and no softening of the tissue. The less severely diseased areas, especially areas 6, 37 and 7, showed changes somewhat similar to those already described, but in a much less degree; especially, the gliosis in the white and gray matter was much less intensive; many more of the ganglion cells, especially in the third layer, were well preserved; however, the depletion of the second layer and its assimilation with the first layer were well marked. The central area was only insignificantly damaged, and areas 17, 18 and 19 of the occipital lobe were perfectly preserved; likewise, the white matter of the occipital lobe appeared unaltered. There was no gliosis, either in the gray or in the white matter of the occipital lobe.

TABLE 2.—*Clinical and Pathologic Data in 18 Cases*

Case	Time of Examination Post Mortem, Hours	Clinical and Pathologic Data	Differental Ratio of Skull Capacity to Brain Volume, %	Histologic Changes with Special Reference to Neurofibrillar Picture
6	16	Woman, 72 years; senile dementia with focal cortical atrophy (Pick's disease); carcinoma of left breast with metastases to lungs	29.31	Typical case of Pick's disease (focal senile atrophy); abnormal neurofibrillar structures characterized by hyperargyrophilia in Bielschowsky preparations and by hypermineralization in micro-incinerated preparations (see protocol)
9	2	Woman, 35 years; dementia praecox, catatonic type; pulmonary, intestinal and meningeal tuberculosis; subdural hematoma over left hemisphere; emaciation	9.40	Intracellular neurofibrils slightly coarser than usual, in some instances tending to collect along the cell margins; however, they are not overargyrophilic, nor is there formation of strands or rods; general tendency of the nuclei and glia cells to stain slightly darker than usual; no plaques
10	11	Man, 65 years; dementia praecox; arteriosclerosis of aorta, cardiac valves and kidneys; frontal convolutions somewhat narrower than usual	10.96	Normal neurofibrillar picture; no plaques
11	15½	Woman, 76 years; psychosis and parkinsonian syndrome with cerebral arteriosclerosis; generalized arteriosclerosis	8.82	Normal neurofibrillar picture; no plaques
12	57	Man, 66 years; psychosis with cerebral arteriosclerosis; convulsive seizures; adenocarcinoma of the prostate with metastases (grade 4); bronchopneumonia	2.26	Normal neurofibrillar picture; no plaques
15	19½	Man, 70 years; Korsakoff's psychosis with chronic alcoholism; generalized arteriosclerosis; frontal convolutions narrow, sulci wide; hemorrhagic softening in right putamen and right caudate nucleus	12.09	In central regions and occipital lobes, normal Bielschowsky picture; in area 10 and in subiculum of cornu ammonis (area entorhinalis) intracellular neurofibrils of a number of cells appear coarser than normal, many accumulating along edges of cells; no formation of compact strands; nuclei of these cells and, to a lesser degree, of a few neighboring glia elements, appear abnormally argyrophilic; no plaques
16	13	Man, 29 years; dementia praecox, paranoid type; death 12 hours after poisoning with household lye; severe burns of face, mouth, trachea, bronchi, esophagus and stomach; perforation of esophagus; hemorrhagic mediastinitis; pulmonary edema; cerebral edema; gyri flattened, sulci reduced to lines	—1.07	Normal neurofibrillar picture; no plaques
17	2	Man, 71 years; parkinsonian syndrome; generalized arteriosclerosis; generalized cortical atrophy, most marked in both frontal lobes; hydrocephalus internus (ex vacuo); central white matter atrophic, markedly decreased in amount	12.29	In area 10 and in occipital lobes, consistently throughout all specimens made, a mild "soaking change" is seen; nuclei of a great number of nerve and glia elements stained dark; neurofibrils of some of these cells adherent to and aggregated along edges of cells, while other cells in these regions appear normal; in a few instances some hyperargyrophilic clumps and short rods can be seen in these cells; no Alzheimer strands; no senile plaques
18	29¾	Woman, 61 years; dementia praecox, catatonic type; generalized arteriosclerosis, hypertension, nephrosclerosis; subarachnoid hemorrhage, covering base and convexity on both sides, from ruptured aneurysm of basilar artery; frontal convolutions somewhat narrower than usual, the others flattened	1.11	In area 10 considerable "soaking change" of most cellular elements; increased argyrophilia of nuclei of nerve and glia elements; formation of thickened argyrophilic strands (fig. 23C), rods and crumbs in cytoplasm of ganglion cells; some strands winding, but none of as smooth and even outline as in Alzheimer's disease; some ganglion cells show normal neurofibrillar picture; no plaques; most ganglion cells in central region, cornu ammonis and subiculum and many ganglion cells in areas 17 and 18 show normal neurofibrillar picture, while other ganglion cells exhibit "soaking change"

picture, while other ganglion cells exhibit "soaking change"

21	9	Woman, 36 years; psychoneurosis, hysteria; suicide by hanging; death after 45 minutes; subpleural petechial hemorrhages; congestion of kidneys; cerebral edema; gyri flattened, sulci reduced to lines	—1.50	"Water change" (Nissl) in the Nissl picture; "soaking change" in Bielschowsky preparations; hyperargyrophilic strands and rods appear hypermineralized in microincinerated preparations (see protocol)
23	3¾	Woman, 75 years; senile psychosis; generalized arteriosclerosis; coronary atheromatosis; bronchopneumonia; cerebral atrophy, especially of frontal, central and parietal regions	11.52	Arteriosclerosis and arteriolosclerosis of the brain; no senile plaques; intracellular neurofibrils normal
24	14	Man, 65 years; psychosis with cerebral arteriosclerosis; seizures; generalized arteriosclerosis, coronary occlusion; atrophy of frontal lobes and convolutions surrounding sylvian fissure; small focus of softening in left red nucleus and in basal part of optic thalamus	10.32	Nissl specimens: area 10 and central region: Meninges thickened but not infiltrated; fibrosis of small cortical blood vessels, but without hyalinization or other form of degeneration of their walls; cortex in other respects normal in architecture and cytologic structure. Areas 17 and 18: In area 18 a few small vascular lesions in outer cortical layers (2 and 3); ganglion cells here rarified and replaced by loosely arranged gliosis, while small and middle-sized cortical blood vessels stand out; gliosis replacing these small defects is astrocytic, protoplasmic and fibrillary. Bielschowsky specimens: Neurofibrillar picture of the preserved cortical ganglion cells normal
27	7½	Man, 45 years; imbecility, with congenital spastic diplegia; death from intestinal obstruction (operation) 2 days after onset; dilatation and early perforation of descending colon; bronchopneumonia; frontal convolutional atrophy; marked hydrocephalus internus with destruction of septum pellucidum; marked thinning of both internal capsules	.....	In area 10 the neurofibrils somewhat coarser than usual and slightly overargyrophilic; no formation of strands observed; nuclei of these cells show tendency to stain somewhat darker than usual; other parts of brain (area 17, central area and putamen) show normal neurofibrillar picture
28	2	Woman, 74 years; senile dementia Alzheimer type (Alzheimer's disease)	13.86	Typical case of Alzheimer's disease; hyperargyrophilic Alzheimer strands of diseased ganglion cells appear hypermineralized in microincinerated preparations (see protocol)
30	4½	Man, 72 years; chronic paranoid psychosis with chronic alcoholism; polyneuritis with weakness, ataxia and areflexia of both legs; history of Jamaica ginger (triorthocresyl phosphate) poisoning 5 years before; coronary sclerosis and occlusion; atrophy of frontal lobes; degeneration of anterior horns of lumbar cord	15.12	Ganglion cell disease of pellagral type; thickened meshes of honeycombed neurofibrillar network appear hyperargyrophilic in Bielschowsky preparations and hypermineralized in microincinerated preparations (see protocol)
31	20	Man, 34 years; manic-depressive psychosis; gastric ulcer with hemorrhage; brain pale, in other respects of normal appearance	3.79	Normal neurofibrillar picture
32	17	Woman, 40 years; psychosis complicating cardiovascular and renal disease; seizures with tonic rigidity; chronic nephritis, hypertension, pseudouremia (nonprotein nitrogen 29 mg., later 42 and 45 mg.); nephrosclerosis, hepatitis, hypertrophy of the heart; cerebral edema; gyri flattened, sulci reduced to lines; hemorrhagic softening in left occipital lobe	—7.83	Normal neurofibrillar picture
33	7	Woman, 44 years; mental deficiency with psychosis; arteriosclerosis, hypertension, chronic nephritis; moderate cerebral edema; gyri of centroparietal, temporal and occipital regions flattened, sulci narrow; in frontal region gyri narrow	1.15	Normal neurofibrillar picture

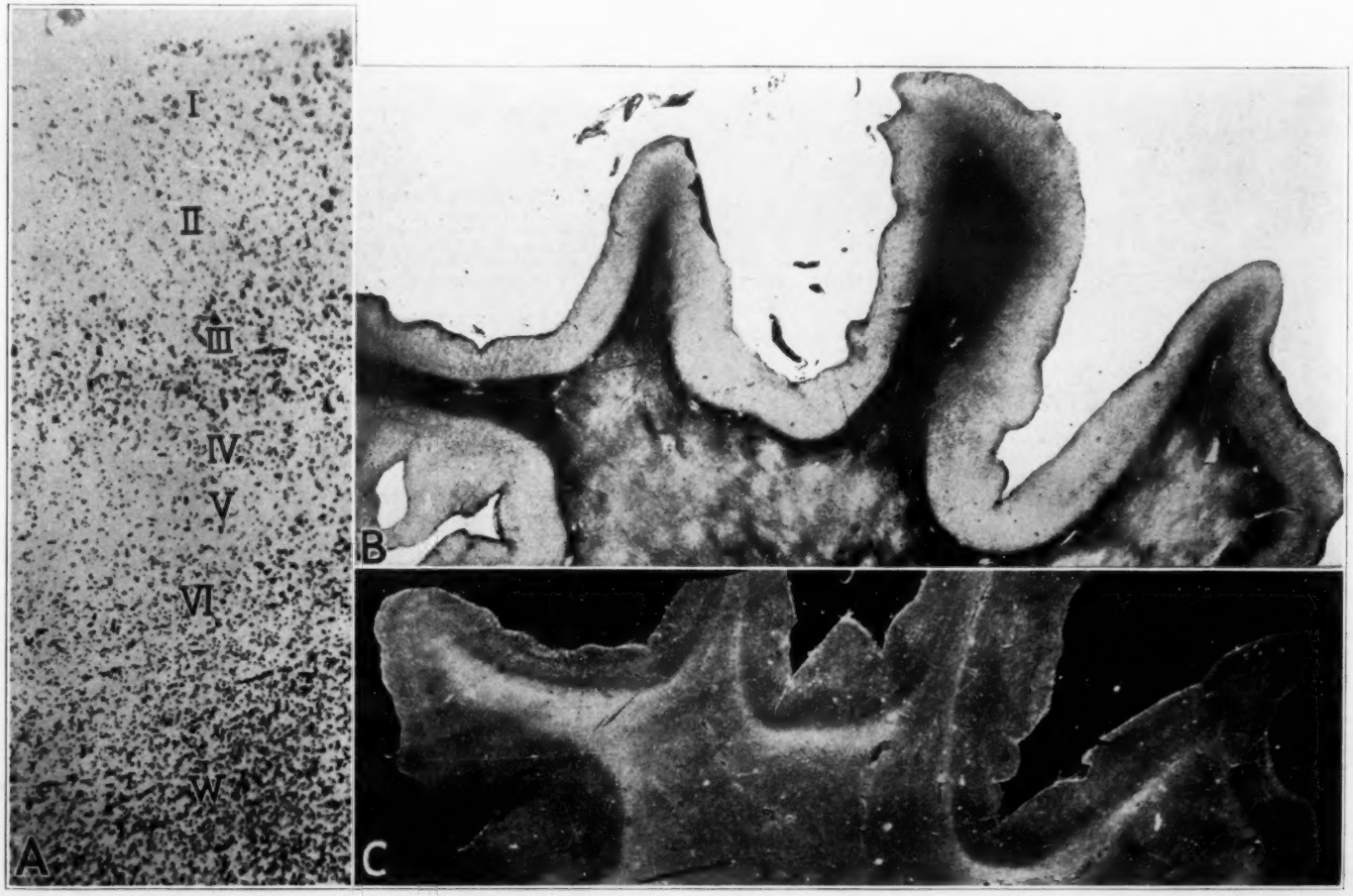

Fig. 1. (case 6).—Pick's disease. *A*, low power view (× 81) of the cortical gray matter of area 10. *W* indicates the convolutional white matter. Layers of the gray matter are marked by corresponding figures. Nissl stain. *B*, low power view (× 5) of the cortex and subcortical white matter of area 10. Masson's trichrome stain. *C*, section (× 4.8) neighboring that seen in *B*. Microincineration; oblique transillumination.

Bielschowsky Preparations: There were a moderate number of senile plaques in area 17 and a few isolated ones in area 6. These plaques consisted of more or less round, sharply localized areas of disarrangement and increased density and argyrophilia of the glial reticulum (figs. 8 and 9). In the areas in which a homogeneous center had been differentiated from the reticular corona, this center

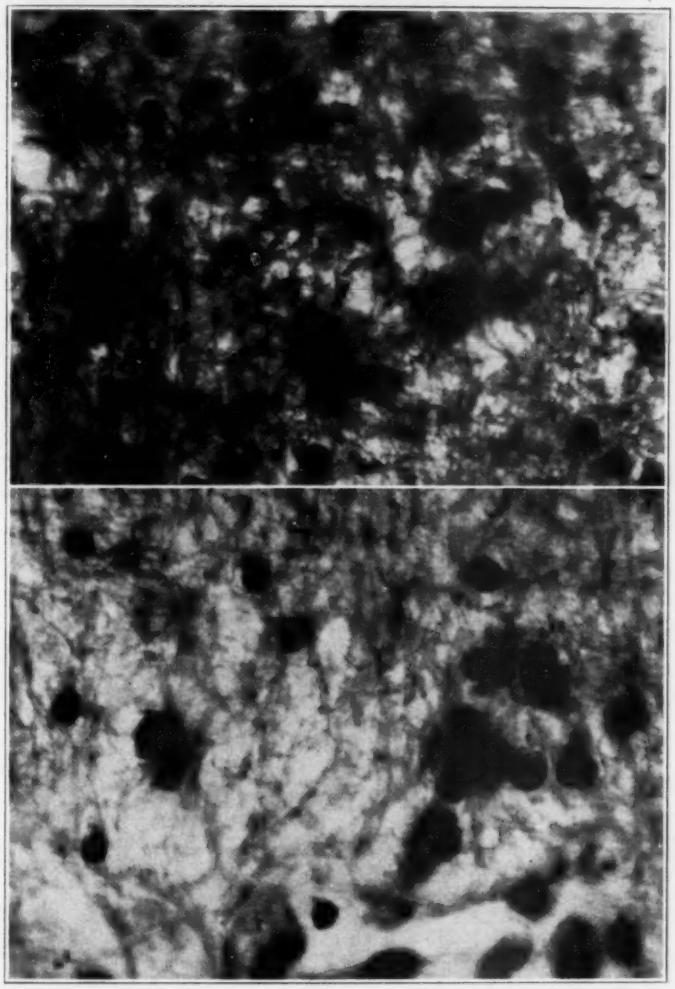

Fig. 2 (case 6).—Pick's disease. High power views (× 584) of the subcortical white matter of area 10. Note the dense astrocytic and oligodendroglial gliosis. Masson's trichrome stain.

appeared hyaline and nonargyrophilic. Areas 10 and 37, area centralis and the cornu ammonis were free from senile plaques.

The neurofibrillar picture of the shrunken cells in the most severely damaged regions (areas 10 and entorhinalis) included several types of alterations. Some

view (× 5) of the cortex and subcortical white matter of area 10. Masson's trichrome stain. *C*, section (× 4.8) neighboring that seen in *B*. Microincineration; oblique transillumination.

cells showed increased coarseness and argyrophilia of the neurofibrils, which at the same time were arranged in a honeycombed, netlike pattern, with rather sharp angulations (fig. 10 *A*). The individual components of this net were definitely thickened, measuring 0.78 micron in diameter, but there was no strand formation in these cells. In others of the shrunken cells the cytoplasm appeared to be taken up by confluent, thick hyperargyrophilic rods and strands, which in some of the cells were uniformly distributed throughout the cytoplasm and in their general arrangement somewhat resembled the normal neurofibrillar pattern (fig. 4 *C*); in others, however, they were thicker (up to 2.6 microns in diameter), more massive and very irregular in shape and outline and appeared to accumulate along the edges

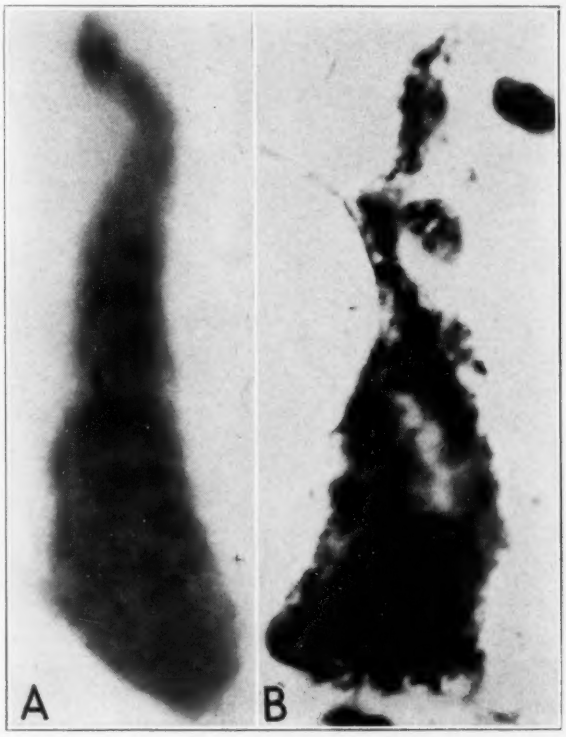

Fig. 3 (case 6).—Pick's disease. *A*, shrunken ganglion cell from the third cortical layer of area 10. Nissl stain; oil immersion, × 2,500. *B*, shrunken ganglion cell from the third cortical layer of area 6. Bielschowsky's silver impregnation; oil immersion, × 1,900.

of the cells (fig. 3 *B*). In none of the cells, however, were winding Alzheimer strands observed. The nuclei of these cells were deformed, shrunken, elongated or round and highly argyrophilic. The neurofibrillar pattern of the swollen cells in the severely damaged areas showed similar alterations. In the milder forms the center of the cells was taken up by a similar honeycombed network, as in the first group of shrunken cells described here; however, the network was wider, having the appearance rather of a wire grating (fig. 4 *D*), while along the edges argyrophilic masses (balls, rods or marginal strands) were observed (fig. 4 *D*).

In other, more severely swollen cells the central network was incomplete and preserved only near the edges (fig. 4 *B*), or was destroyed and replaced by homogeneous, nonargyrophilic material (fig. 5 *B*). The nuclei of these cells were shrunken, deformed (triangular), highly argyrophilic and displaced toward the edges of the cell. In addition to these changes in obviously diseased cells, there was also general increased argyrophilia of the tissue throughout all the specimens examined, involving the axis-cylinders, dendrites and neuronal and glial nuclei.

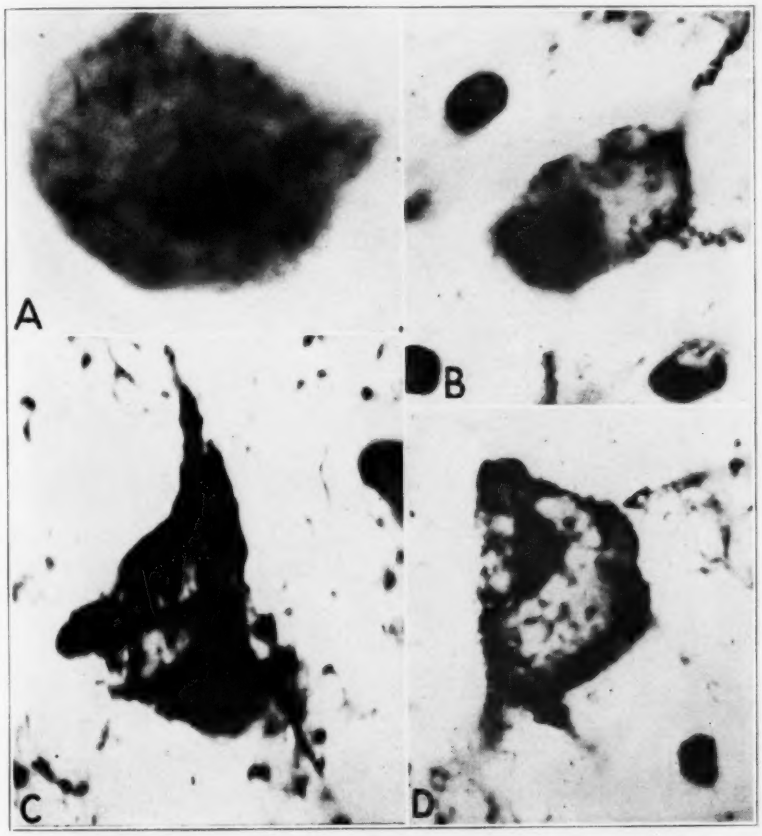

Fig. 4 (case 6).—Pick's disease. *A*, a swollen ganglion cell from the third cortical layer of area 10. Nissl stain; oil immersion, × 2,500. *B*, a swollen ganglion cell from the third cortical layer of area 10; *C*, a shrunken ganglion cell from the third cortical layer of area 6, and *D*, a moderately swollen ganglion cell from the third cortical layer of area 10. Bielschowsky's silver impregnation; oil immersion, × 1,900.

The neurofibrillar picture of the less severely damaged areas (6, 37 and 7 and fields H_4, H_3 and H_2 of the cornu ammonis) showed similar changes, but to a much less degree. Although here, also, many of the larger cells showed argyrophilic nets or marginal argyrophilic strands and nuclei, many showed

normal neurofibrils, and nuclei which stained only faintly with silver. The central area and area 17 showed a similar change, though only an indication of it. A few of the pyramidal ganglion cells showed shrinkage; a few, swelling of the Pick type. The latter showed thickening and the wire-grating appearance of the fibrils.

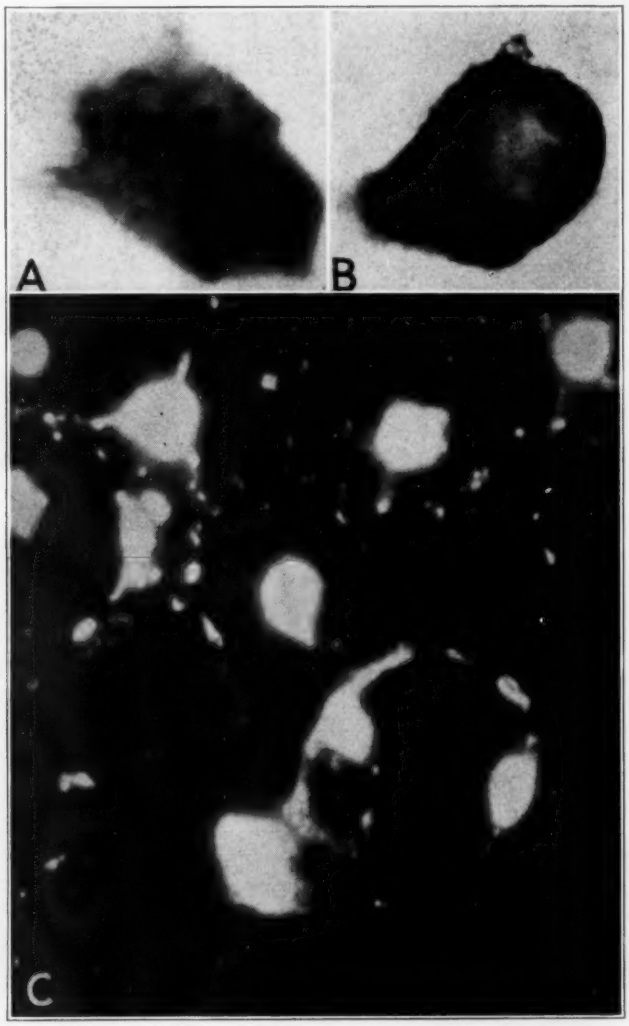

Fig. 5 (case 6).—Pick's disease. *A*, a swollen ganglion cell from the third cortical layer of area 10. Nissl stain; oil immersion, × 2,500. *B*, a swollen ganglion cell from the third cortical layer of area 10. Bielschowsky's silver impregnation; oil immersion, × 1,900. *C*, a swollen ganglion cell and a number of oligodendroglia and microglia cells and fibrillary astrocytes from the third cortical layer of area 10. Microincineration; dark field illumination; × 2,500.

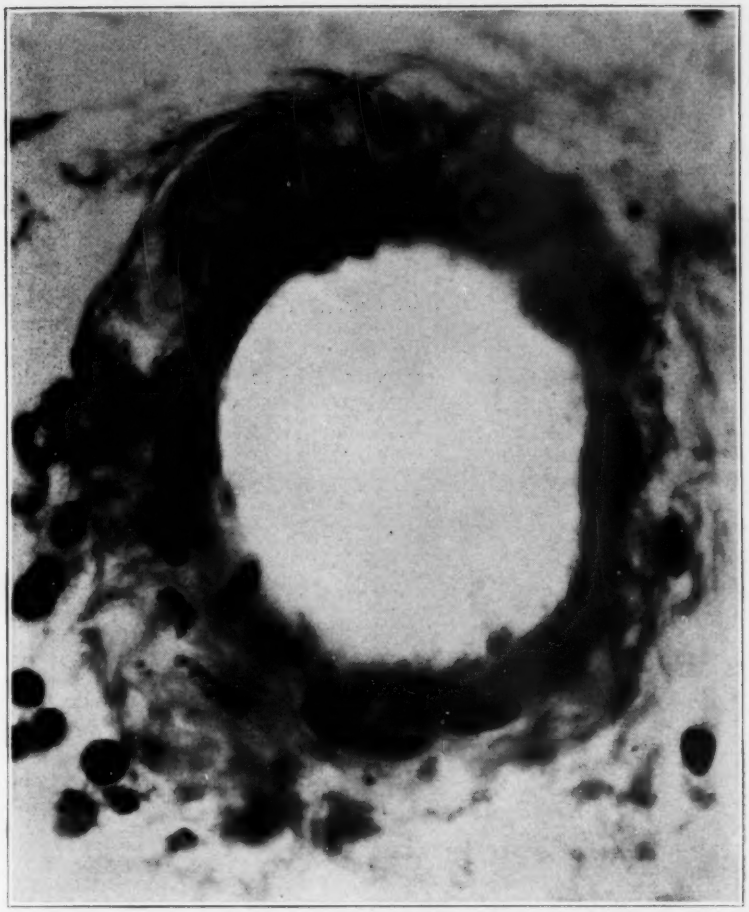

Fig. 6 (case 6).—Pick's disease. An arteriole from the subcortical white matter of area 10. Note thickening and hyalinization of the intima and media. Masson's trichrome stain; × 1,167.

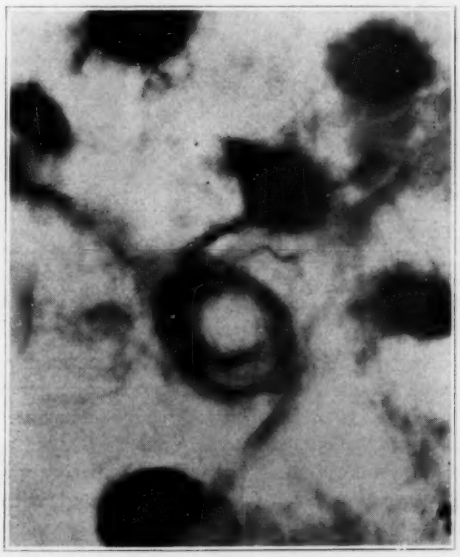

Fig. 7 (case 6).—Pick's disease. A capillary from the second cortical layer of area 10. Note thickening and hyalinization of its wall, including the endothelial lamella and the ground membrane, which are especially marked where glial sucker feet are attached to it. Masson's trichrome stain; oil immersion, × 2,000.

Microincinerated Preparations: All the changes found expression in alterations of the ash picture as well. At a low magnification, the cortical gray ribbon in sections from area 10, as a whole, appeared demineralized by the loss of ganglion cells (fig. 1 *C*). The third layer alone retained a great deal of its normal ash residue, contained in the ganglion cells, a considerable number of which were preserved in this layer; the first layer appeared hypermineralized in many places, due to the astrocytic gliosis. In the other layers, also, the proliferating glia cells showed a high mineral content, but the gliosis was not sufficiently intensive to cause the appearance of an increased ash content in these

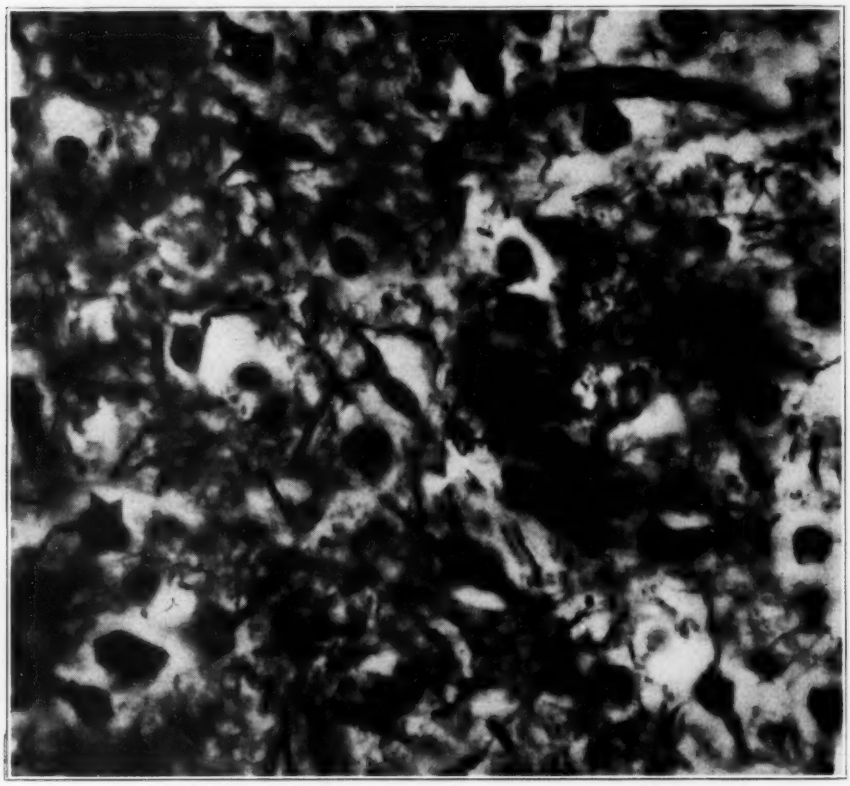

Fig. 8. (case 6).—Senile plaque in a case of Pick's disease; area 17, the second cortical layer. Note that the reticulum in the plaque (right half of the figure) is denser, but of finer caliber, than the glial reticulum of the surrounding normal tissue. Bielschowsky's silver impregnation; × 1,000.

layers, since the depletion in ash due to the disappearance of ganglion cells was greater. The demineralization of the central white matter was only slight and was not fully correlated with the demyelination (compare figure 1 *C* with the neighboring Masson preparation shown in figure 1 *B*). The marmorated pattern of the demyelination was not expressed in the neighboring microincinerated preparation; the ash picture, however, was well correlated with the distribution of the gliosis in the white matter; small areas of perivascular hypermineralization

(fig. 1 *C*) corresponded to perivascular areas of more intensive gliosis. Most marked was the hypermineralization of the white matter bordering on the gray matter, corresponding to the intensive gliosis in this region (fig. 11, compare with figure 1 *A*). Most of the mineral here was contained in the nuclei of the proliferating glia cells (mainly oligodendroglia cells and astrocytes), much less

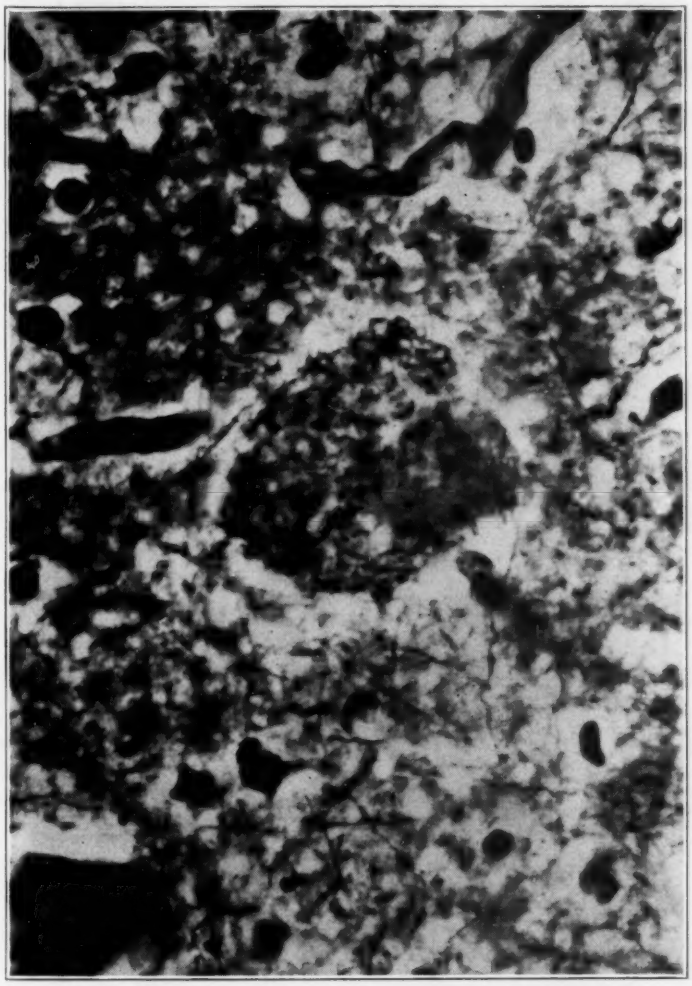

Fig. 9 (case 6).—Senile plaque in case of Pick's disease; area 17, the second cortical layer. Note that the reticulum in the plaque is denser, but of finer caliber than the glial reticulum of the surrounding normal tissue. Bielschowsky's silver impregnation; × 929.

in the myeloaxostroma and the supporting glial reticulum of the preserved myelinated fibers. This is well demonstrated in figure 11, which shows at higher magnification the fifth and sixth cortical layers and the adjacent convolutional white matter of the section illustrated in figure 1 *C*. It also shows well the

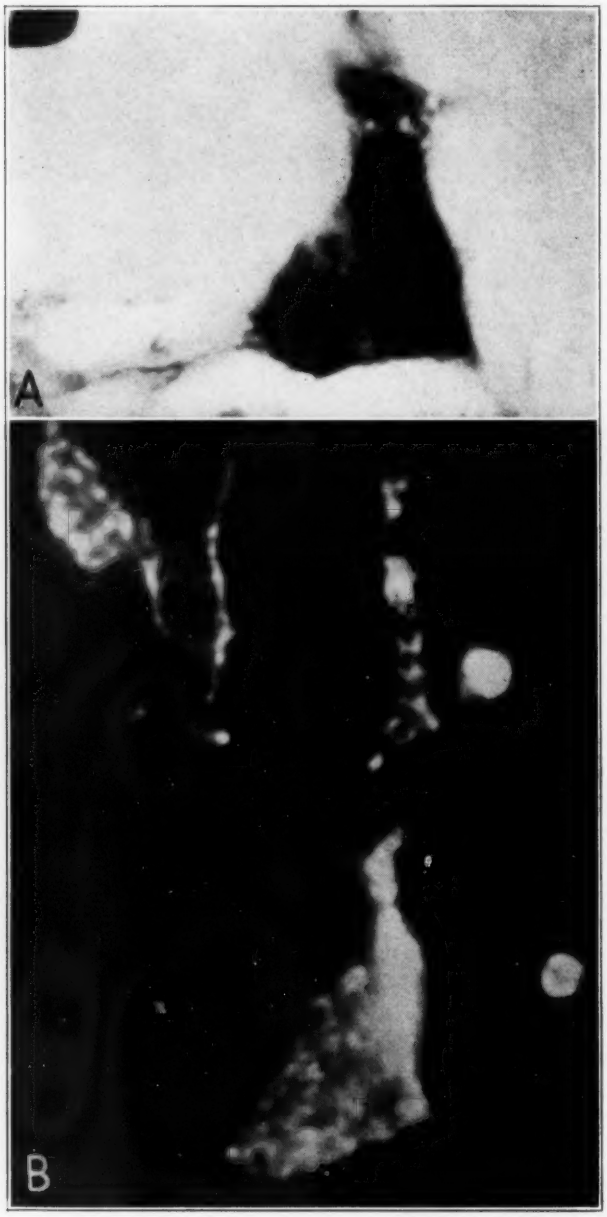

Fig. 10 (case 6).—Pick's disease. Shrunken ganglion cells from the third cortical layer of area 10. *A*, Bielschowsky's silver impregnation; oil immersion, × 1,900. *B*, microincineration; dark field illumination; × 2,500.

demineralization of the fifth and sixth cortical layers, due to the depletion of ganglion cells; the only mineral present in these layers was contained in the nuclei and the cytoplasm of the loosely arranged, not intensely proliferating microglia cells and astrocytes.

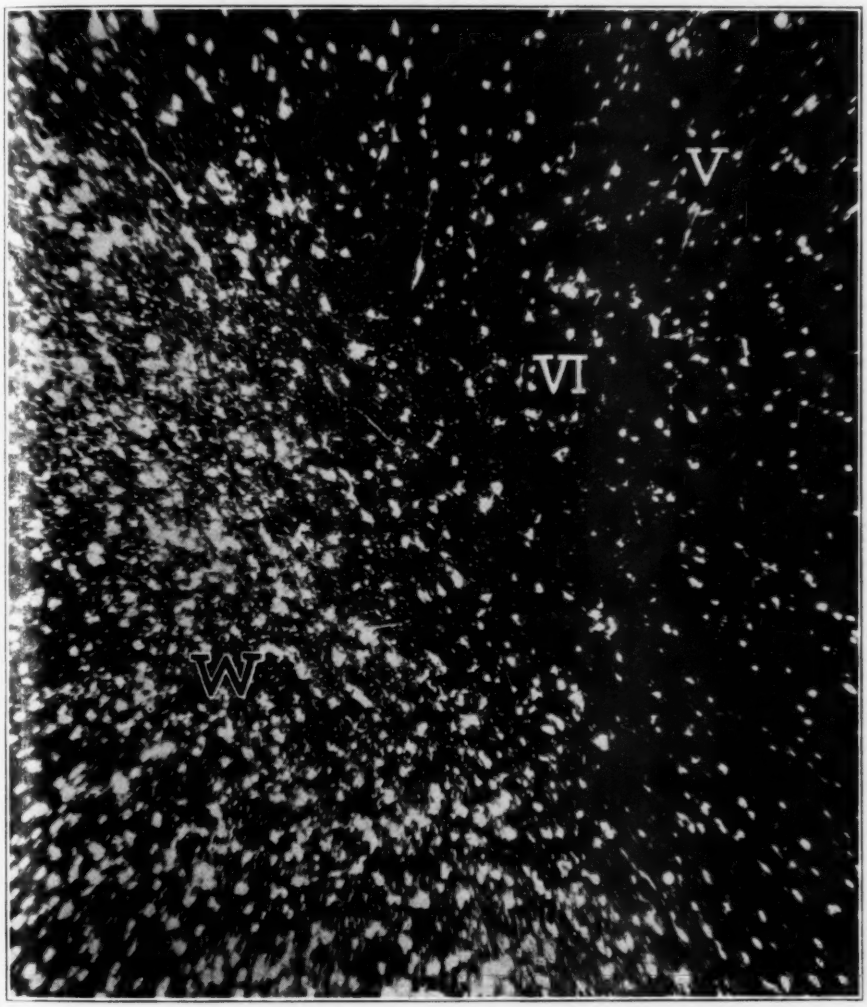

Fig. 11 (case 6).—Pick's disease. The fifth and sixth cortical layers and the convolutional white matter (*W*) of area 10. Note demineralization of the fifth and sixth layers, due to depletion of the ganglion cells, and hypermineralization of the convolutional white matter, due to the increase in nuclei and processes in intense gliosis. Microincineration; dark field illumination; × 180.

The thickened neurofibrillar network and the thickened marginal strands of the shrunken ganglion cells appeared hypermineralized in microincinerated preparations (compare figure 10 *B* with figures 3 *B* and 10 *A*); the same was true for the marginal strands of the swollen ganglion cells (compare figures 5 *B* and *C*).

A number of proliferating microglia cells in the gray matter contained cytoplasmic iron, which was most marked in Sommer's sector of the cornu ammonis and slightly less in the area entorhinalis.

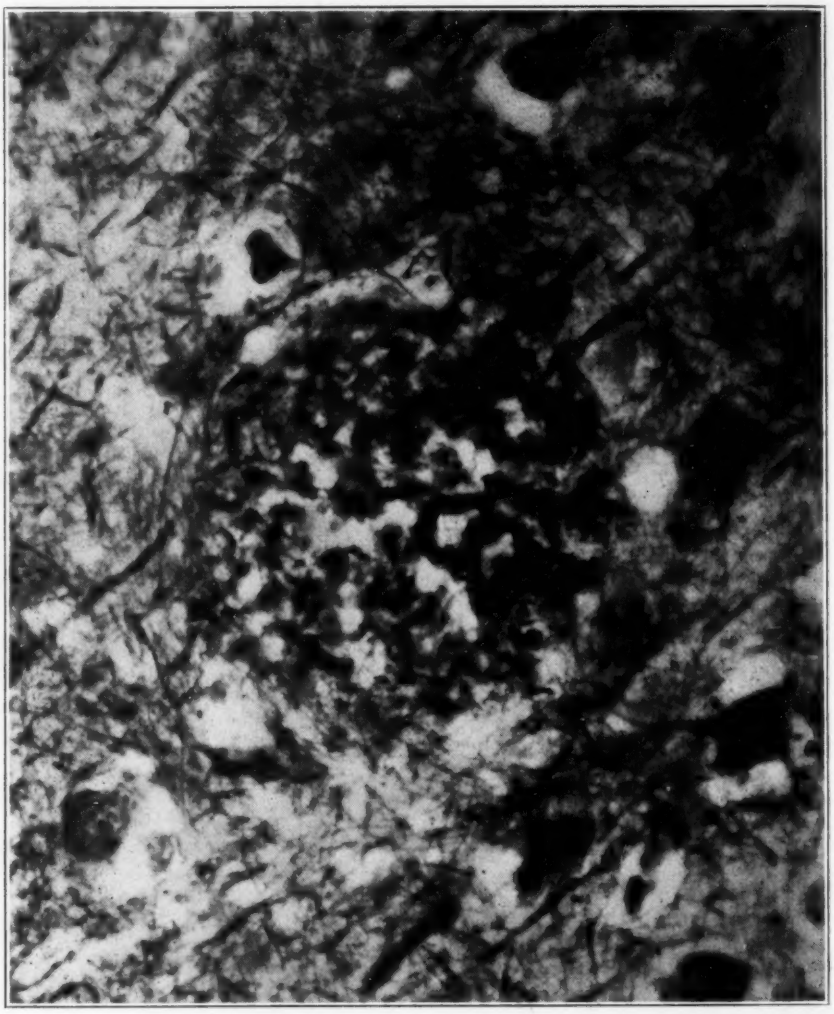

Fig. 12 (case 28).—Senile plaque in a case of Alzheimer's disease; area centralis, the second cortical layer. Bielschowsky's silver impregnation; × 929.

CASE 28.—*Alzheimer's disease (focal cerebral atrophy, type Alzheimer).*

Clinical Note.—A woman aged 74 with senile dementia (Alzheimer's disease) was delirious, disoriented, confused, amnesic and confabulatory; she spoke ceaselessly in a mumbling, monotonous voice, and speech was almost unintelligible; only a chance phrase could be overheard and correctly interpreted. There was motor restlessness, constant picking at the bedclothes, or restless wandering about

the ward in an aimless fashion. No neurologic changes, especially no reflex changes, were detected. Death resulted from bronchopneumonia.

Autopsy.—The brain showed severe atrophy; the convolutions were narrowed throughout, most markedly in the frontal lobes. The sulci were wide and in some places formed wide gaps. The basal arteries, especially the arteries of the circle of Willis, were free from arteriosclerosis.

The aorta, coronary arteries and kidneys showed arteriosclerotic changes; the lungs, bronchopneumonia and edema.

Microscopic Examination.—There were numerous senile plaques in the cornu ammonis (especially in field H_4), in areas 17 and 18, in the central region and in the island of Reil. The plaques consisted of localized, sharply circumscribed

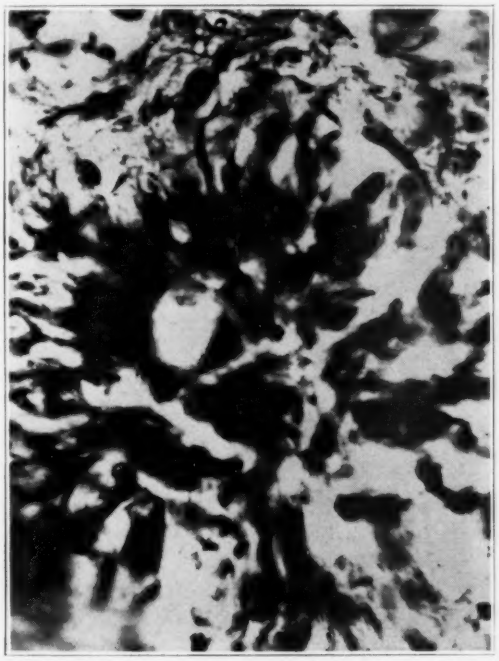

Fig. 13 (case 28).—A wheel-like or cudgel-shaped senile plaque from field H_4 of the cornu ammonis, in a case of Alzheimer's disease. The center of the plaque is occupied by a precapillary blood vessel (probably a venule); the radiating spikes are thickened, hypertrophied, hyperplastic and deformed (metaplastic) hyperargyrophilic macroglial sucker feet. Bielschowsky's silver impregnation; oil immersion, × 900.

alterations of the glial reticulum, which here appeared coarser, increasedly argyrophilic, more wide meshed and less dense than outside the plaques and showed bizarre deformities, such as clubs, buds, dots and strands of varying shape and curvature (fig. 12). In some places, especially in the cornu ammonis and the occipital lobes, the elements composing the plaques showed a rosette-like arrangement, resembling a cudgel (fig. 13). In 1 instance (in the central region) a plaque was seen to surround a necrotic (pyknotic and homogenized) pyramidal

Fig. 14 (case 28).—Senile plaque in a case of Alzheimer's disease; area centralis, the third cortical layer. Note the pyknotic ganglion cell in the center of the plaque. Bielschowsky's silver impregnation; × 286.

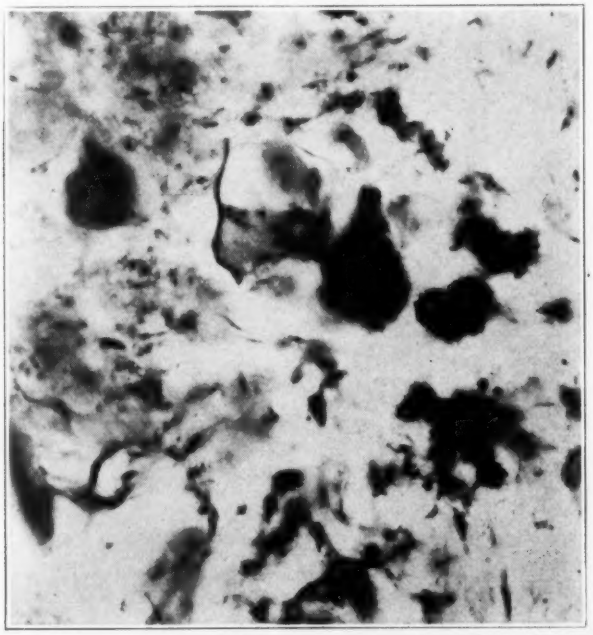

Fig. 15.—Center of the senile plaque containing a pyknotic ganglion cell from the specimen reproduced in figure 14, at higher magnification. Bielschowsky's silver impregnation; oil immersion, × 1,900.

ganglion cell (figs. 14 and 15). There were numerous diseased ganglion cells typical of the Alzheimer change, presenting winding, hyperargyrophilic, solid strands with smooth, even outline, most of them measuring from 2.6 to 3.68 microns in diameter (figs. 16 *C* to 19 *D*). Most of them were observed in the proximal part of the subiculum of the cornu ammonis itself (area entorhinalis) and an only slightly smaller number in the cornu ammonis, the central region, the island of Reil and areas 10, 17 and 18. In most of the slides of these regions the ganglion

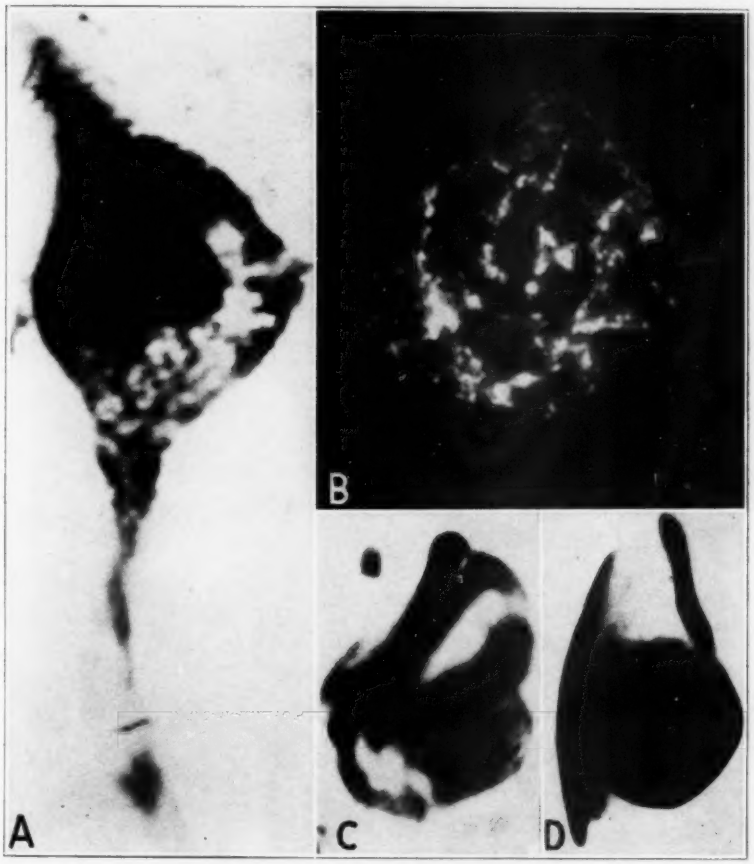

Fig. 16.—*A* (case 30), central neuritis (neuronitis) of pellagral type, in a case of alcoholic paranoid psychosis with polyneuritis. A swollen ganglion cell from the subiculum of the cornu ammonis (area entorhinalis). Bielschowsky's silver impregnation; oil immersion, × 1,900.

B (case 30), cell similar to that reproduced in *A*, from a neighboring block of tissue from the subiculum of the cornu ammonis (area entorhinalis). Microincineration; dark field illumination; × 2,000.

C and *D* (case 28), two ganglion cells from the subiculum of the cornu ammonis, showing Alzheimer's ganglion cell disease. Bielschowsky's silver impregnation; oil immersion, × 1,900.

cells adjacent to the Alzheimer cells presented a normal neurofibrillar picture (fig. 19 *D*); also, all nuclei were light and unstained; in some of the less severely affected cells, in addition to the Alzheimer strands, normal neurofibrils could be seen (fig. 19 *A* and *B*).

There were, however, a few slides in which a staining artefact had taken place (fig. 20 *A*); all nuclei were dark and argyrophilic, and no normal neurofibrils were stained, either in the normal or in the mildly affected cells. In these cells the cytoplasm was light, hyaline, homogeneous pinkish brown (fig. 20 *A*).

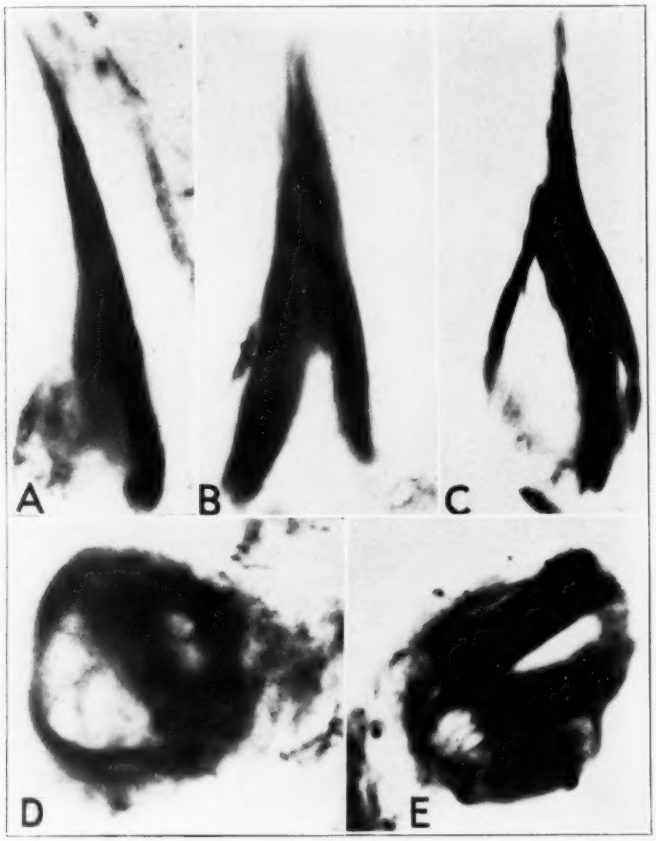

Fig. 17 (case 28).—Ganglion cells from the subiculum of the cornu ammonis (area entorhinalis), in a case of Alzheimer's disease, showing various types of Alzheimer's ganglion cell disease with typical strand formation. See the description in the text. Bielschowsky's silver impregnation; oil immersion, × 1,900.

The typical Alzheimer strands of neighboring diseased cells, however, stained well in these preparations (fig. 20 *A*), sometimes even somewhat better, darker and in more contrast than in correctly stained preparations. No other argyrophilic changes in the cytoplasm, especially no rods or crumbs, appeared in these preparations. This showed that the optimal staining conditions of the Alzheimer strands and those of

the normal neurofibrils are fundamentally different. An explanation may be found in a chemical difference, demonstrated by Alexander and Myerson,[23] namely, in the fact that normal neurofibrils are free from heat-resistant mineral, while Alzheimer strands contain ample amounts of heat-resistant, water-insoluble mineral (fig. 18 *B*, compare with *A*).

The putamen showed neither senile plaques nor neurofibrillar changes.

CASE 30.—*Pellagral ganglion cell disease in chronic alcoholic psychosis with polyneuritis.*

Clinical Note.—A man aged 72 with chronic paranoid psychosis associated with chronic alcoholism presented polyneuritis, with weakness, ataxia and areflexia

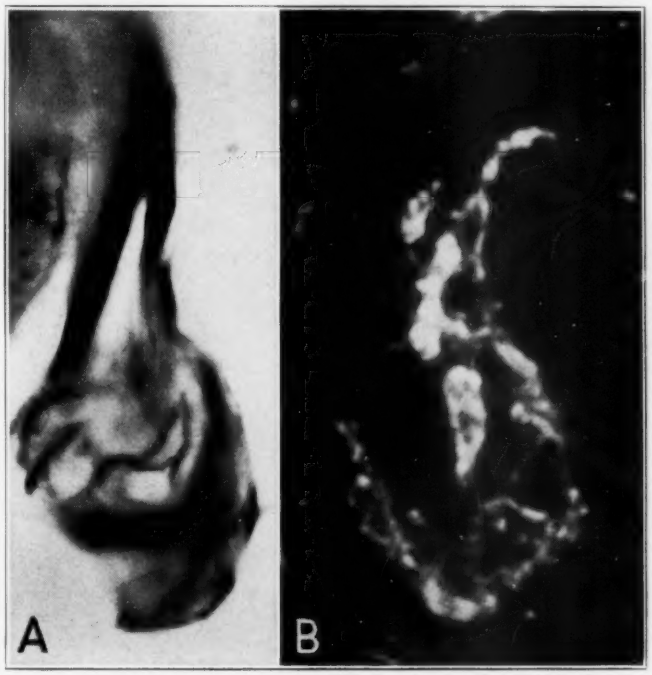

Fig. 18 (case 28).—Two diseased ganglion cells similar to those shown in figure 17, from neighboring blocks of tissue from the subiculum of the cornu ammonis (area entorhinalis), in a case of Alzheimer's disease. *A*, Bielschowsky's silver impregnation; oil immersion, × 1,900. *B*, microincineration; dark field illumination; × 1,900. Note the deposits of heat-resistant mineral ash corresponding to the winding Alzheimer strands (compare *A* and *B*).

of both legs. There was a history of Jamaica ginger (triorthocresyl phosphate) poisoning five years before. Sudden death occurred from coronary occlusion.

Autopsy.—There were: atrophy of both frontal lobes of the brain; degeneration of the anterior horns of the lumbar region of the spinal cord; coronary sclerosis and occlusion; atheromatosis of the aorta, and chronic passive congestion of the liver.

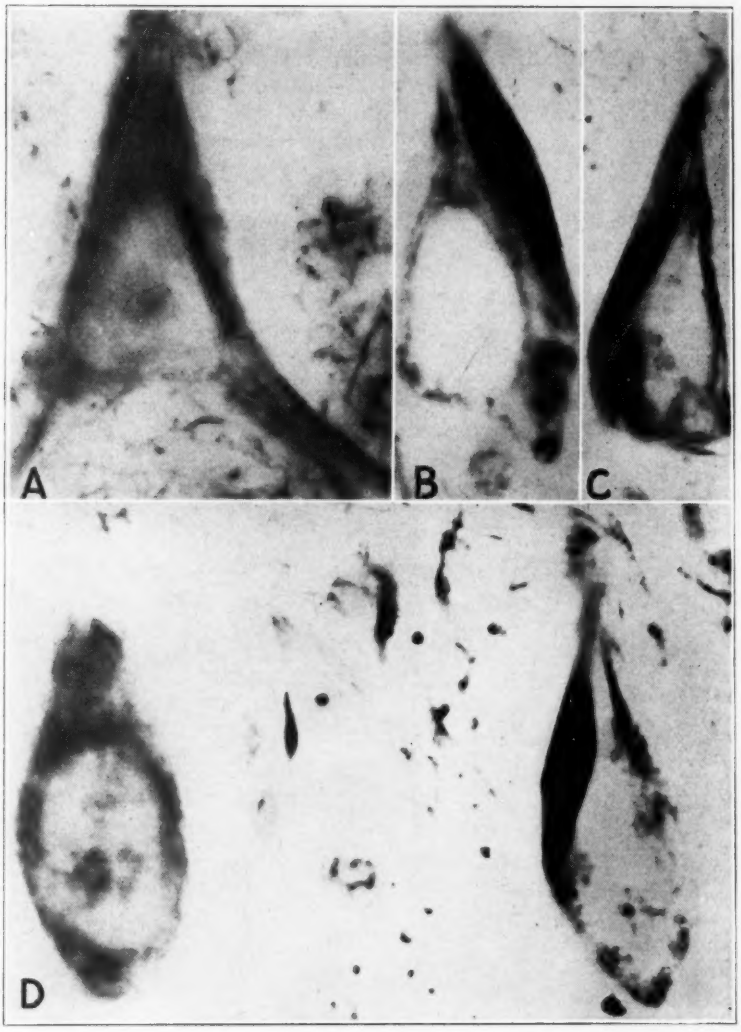

Fig. 19 (case 28).—Photomicrographs in a case of Alzheimer's disease (Bielschowsky's silver impregnation; oil immersion). *A*, ganglion cell showing mild or beginning disease, from the third layer of the precentral area. A hyperargyrophilic Alzheimer strand is visible to the right of the nucleus, along the nuclear membrane, measuring only 1 micron in diameter. The remainder of the cell body shows normal neurofibrillar impregnation. × 1,900.

B, a diseased ganglion cell from the subiculum of the cornu ammonis (area entorhinalis). A massive Alzheimer strand is visible along the right cell margin, extending into the apical dendrite, while the remainder of the cell body shows normal neurofibrillar impregnation. × 1,900.

C, a diseased ganglion cell from the subiculum of the cornu ammonis (area entorhinalis). The upper part of the thick Alzheimer strand along the left cell margin shows neurofibrillar striation, at the transition of the cell body into the apical dendrite. × 1,900.

D, two neighboring ganglion cells, one diseased and one normal, from the subiculum of the cornu ammonis (area entorhinalis), correctly stained. The cell to the left shows a normal neurofibrillar pattern; the cell to the right, Alzheimer's ganglion cell disease. × 1,667.

Microscopic Examination.—Nissl Picture: There were swelling and central tigrolysis of the large pyramidal ganglion cells in the third and fifth layers of the frontal, temporal and occipital lobes (areas 10, 6, entorhinalis, 18 and 19). Nissl-staining material, in granules and small clumps, was visible along the edges of these cells; the nuclei of the cells were deformed and eccentric. Nuclear chromatin

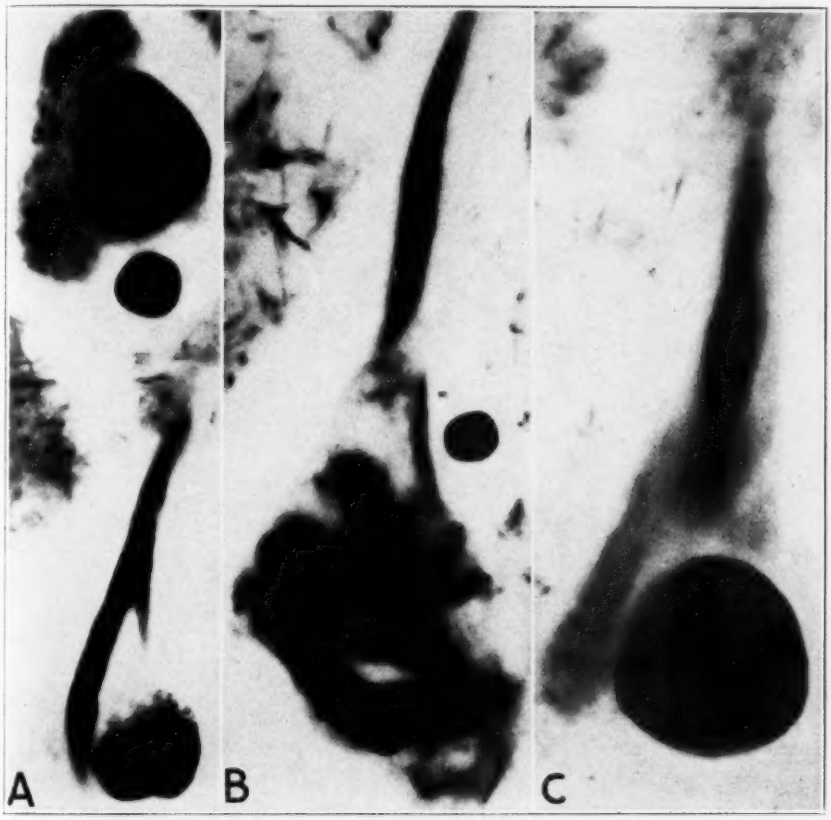

Fig. 20 (case 28).—Photomicrographs in a case of Alzheimer's disease (Bielschowsky's silver impregnation; oil immersion). *A*, two neighboring ganglion cells from the subiculum of the cornu ammonis (area entorhinalis), one diseased and one normal, showing a "staining artefact." The intracellular neurofibrils of the normal cell, in the upper half of the figure, have failed to stain; its cytoplasm is homogeneously pale and its nucleus solid black. The Alzheimer strands of the diseased ganglion cell, however, in the lower half of the figure, are impregnated just as well as in a correctly stained preparation, such as that reproduced in figure 19 *D*. × 1,600. *B*, a diseased ganglion cell from the subiculum of the cornu ammonis (area entorhinalis), showing Alzheimer's strands, partly in whorl formation (in the cell body). × 1,900.

C, a diseased ganglion cell from the subiculum of the cornu ammonis (area entorhinalis), showing a "staining artefact." The nucleus stains homogeneously black; the normal part of the cytoplasm homogeneously pale. The Alzheimer strand, however, in the atypical dendrite, is well impregnated (compare with figure 17 *A*, from a correctly stained preparation). × 1,900.

was denser than normal; the nucleolus was eccentric. The picture corresponded to pellegral cell disease, as described by Parhon and Papinian [11] and by Marinesco.

Bielschowsky Picture: The intracellular neurofibrils of the diseased ganglion cells accumulated along the edges of the diseased cells as marginal strands, while the interior of the cells was taken up by a loose, honeycombed network, the meshes of which measured 0.78 micron in thickness (fig. 16 *A*), or was homogeneously pale. The pictures corresponded with those described by Rezza.[13]. The nuclei of the cells were shrunken and elongated, most of them being impregnated to a dark brown tinge.

Microincineration Picture: The thickened meshes of the honeycombed neurofibrillar network, which appeared hyperargyrophilic in Bielschowsky preparations, were hypermineralized (figs. 16 *B* and 21).

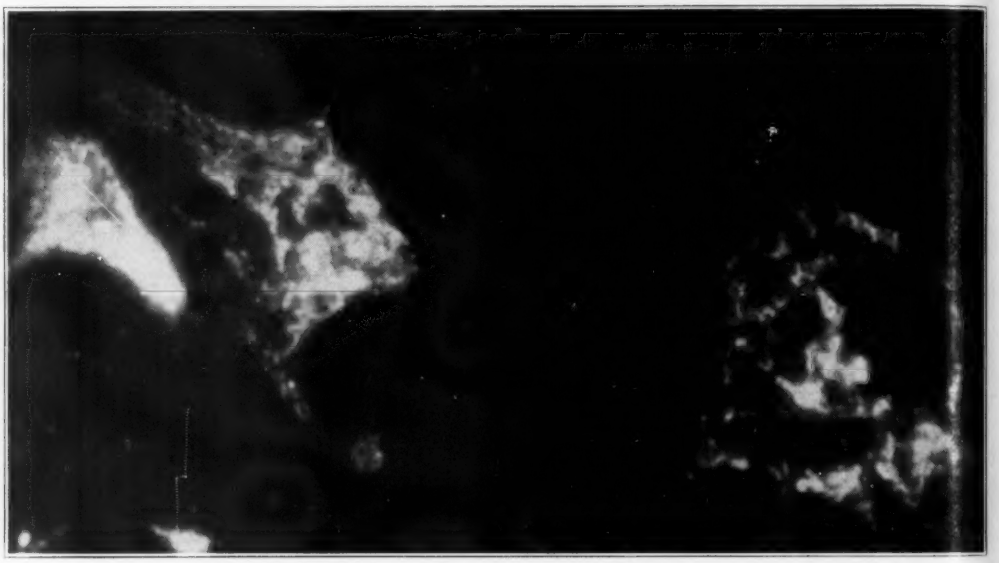

Fig. 21 (case 30).—Central neuritis (neuronitis) of pellagral type in a case of alcoholic paranoid psychosis with polyneuritis. Three ganglion cells from the subiculum of the cornu ammonis (area entorhinalis) are shown. The two ganglion cells to the left are normal; the one to the right shows swelling (pellagral cell disease) with change in distribution of heat-resistant mineral ashes. Microincineration; dark field illumination; × 2,000.

CASE 21.—*"Water change" (Nissl) and "soaking change" observed in an edematous brain in a case of suicide by hanging.*

Clinical Note.—A woman aged 36 had a psychoneurosis of hysterical type. She committed suicide by hanging; death occurred after forty-five minutes.

Autopsy.—There was severe cerebral edema; the gyri of the hemispheres were flattened and the sulci reduced to lines. There were subpleural petechial hemorrhages and congestion of the kidneys.

Microscopic Examination.—Nissl Picture: Except for the large cells in the third and fifth layers of the central region, the cells in these specimens showed a definite "water change" (Nissl), in which possibly elements of an early acute ischemic change were hidden; the protoplasm was pale, without distinct Nissl

structure; in many instances it was not sharply outlined and showed irregular perinuclear retraction spaces. The nuclei were light, except in the occipital lobe; here, especially in the area calcarina, small, dark nuclei were surrounded by a narrow rim of pale, shrunken cytoplasm.

Bielschowsky Picture: Subiculum: The neurofibrils were crumbled into small, fine, argyrophilic, dustlike granules, most of them measuring from about 0.52 to 0.78 micron in diameter, but there was no argyrophilia of the nuclei. At a low magnification the appearance was normal.

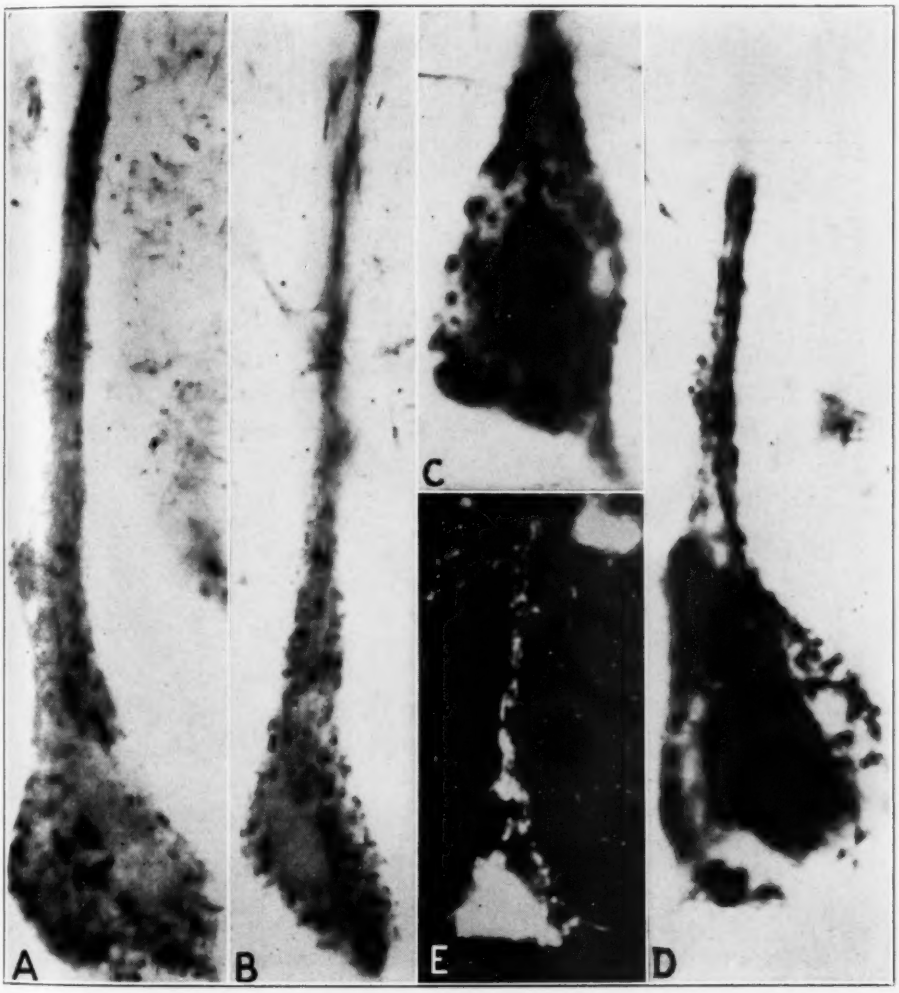

Fig. 22 (case 21).—Sections from an edematous brain in a case of death by hanging. *A* to *D*, Bielschowsky's silver impregnation; oil immersion, × 1,900. *A* and *B*, ganglion cells from the third cortical layer of area 10, showing "soaking change." *C*, ganglion cell from the fifth cortical layer of area 10, showing "soaking change." *D*, ganglion cell from the third cortical layer of the precentral area, showing "soaking change." *E*, ganglion cell from the third cortical layer of the precentral area, similar to that reproduced in *D*, from a neighboring block of tissue; microincineration; dark field illumination; × 1,200.

Central region: Here, there was typical "soaking change," with argyrophilia of the nuclei of the glia and ganglion cells and formation of hyperargyrophilic marginal strands and rods, measuring from 0.78 to 2.6 microns in diameter (fig. 22 *D*). Several sets of specimens were prepared; all of them, although differing in general coloring (some were reddish, others bluish gray), showed the change.

Area 10: Ganglion cells contained fine, dustlike argyrophilic granules and larger globules, measuring from 0.52 to 2.08 microns in diameter (fig. 22 *A*, *B* and *C*). There was no marginal accumulation or formation of strands; normal

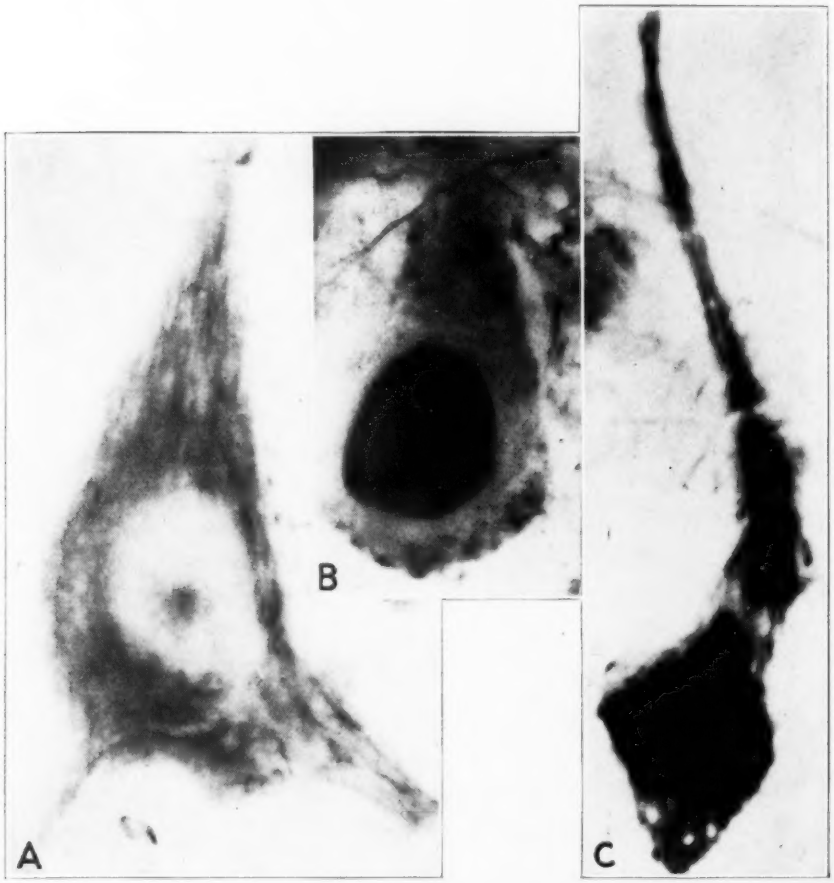

Fig. 23.—Photomicrographs (Bielschowsky's silver impregnation; oil immersion, × 1,900). *A* (case 28), normal ganglion cell from the third cortical layer of the precentral area, correctly stained. *B* (case 28) normal ganglion cell from the subiculum of the cornu ammonis (area entorhinalis), showing a staining artefact. *C* (case 18), ganglion cell from the fifth cortical layer of area 17, showing "soaking change."

fibrils were seen in many of these cells (fig. 22 *A* and *B*). In only scattered places were glia nuclei slightly more argyrophilic than normal. The nuclei of some of the ganglion cells were argyrophilic (fig. 22 *C*); others not (fig. 22 *A* and *B*).

Area 17: Nuclei of ganglion cells were dark and argyrophilic. Intracellular neurofibrils were broken up into small granules and rods, which were slightly hyperargyrophilic; however, there was no formation of strands. Glia nuclei were only moderately argyrophilic; there were no plaques.

Microincineration Picture: The hyperargyrophilic strands, rods and granules were seen to be hypermineralized (fig. 22 *E;* compare with 22 *D*).

COMMENT

Our histologic observations can be divided into three groups: changes concerned with (*a*) the senile plaques; (*b*) the intracellular neurofibrils, with special reference to the relation between the picture presented by Bielschowsky's silver impregnation method and that by microincineration, and (*c*) the special histopathologic changes in Pick's focal senile atrophy.

(*a*) *Senile Plaques.*—These were observed in 2 instances, in the case of Alzheimer's disease (case 28) and, to a much less degree, in that of Pick's disease (case 6). Some of the senile plaques in the case of Pick's disease, which altogether were not numerous, presented an interesting picture. The threads of the silver-stained network, of which they were made up, were not thicker and coarser, as is usually the case, but were thinner and finer than those of the surrounding normal glial reticulum (figs. 8 and 9). In other plaques in this case, however, the network of the plaques was thicker and coarser than the surrounding glial network; also, typical wreath formations with homogenized centers were seen. In the case of Alzheimer's disease the senile plaques were much more numerous; all were composed of a threadwork that was thicker and coarser than that of the surrounding normal tissue (figs. 12, 13, 14 and 15).

The fact that senile plaques exist the threadwork of which is thinner and finer than that of normal glial reticulum convinces us that they cannot be due to impregnation of the glial reticulum with inorganic substances, as von Braunmühl [27] suggested, but that they probably represent the effect of local metaplasia of the glial reticulum itself, due to a process of active growth and leading to transformation of the glial reticulum.

Tissue elements other than the glial reticulum which are incorporated in the plaques are manifold, but are not observed with constant regularity. Cell bodies of enlarged microglia cells were seen in the plaques (fig. 12) or along its edges (figs. 8 and 12). Pyknotic and overimpregnated ganglion cells were seen in the center of some plaques, especially in the frontal and central regions (figs. 14 and 15). Other plaques were arranged around a capillary or a small precapillary blood

27. von Braunmühl, A.: Kolloidchemische Betrachtungsweise seniler und präseniler Gewebsveränderungen: Das hysteretische Syndrom als cerebrale Reaktionsform, Ztschr. f. d. ges. Neurol. u. Psychiat. **142**:1, 1932.

vessel, with abnormally numerous, thickened and overimpregnated macroglial sucker feet, like spikes radiating from a common center, giving a wheel-like or cudgel-like appearance to the plaque (fig. 13). Participation in the plaque of elements other than the glial reticulum, however, was only accidental, although in the literature specific significance has at various times been ascribed to some of them, especially to the microglia cells and pyknotic nerve cells.

The tissue forming the senile plaque ultimately undergoes amyloid degeneration (Hechst,[28] Winkler-Junius [29]); however, it never shows increase or decrease in its content of heat-resistant mineral ashes (Alexander and Myerson [23]).

(*b*) *Intracellular Neurofibrils.*—Normal intracellular neurofibrils, as stained by the Bielschowsky method, are fine, thin solid threads of smooth, even outline, measuring not more than 0.26 micron in width, which stain from a not heavy brown-blackish to a bluish purple shade. In the upper part of the ganglion cell and within the dendrites they are arranged parallel to each other or slightly converging toward the points of the dendrites, while in the basal and lateral part of the cell body their arrangement is more irregular, reminiscent of the wool of sheep or the hair of camels (fig. 23 *A*). The intracellular neurofibrils were normal in all cortical areas examined in 9 cases, that is, in the largest single group in our material, consisting of 2 normal, 3 atrophic and 4 edematous brains; the time of autopsy after death varied from three and three-fourths to fifty-seven hours, with an average of seventeen and one-half hours. In the neighboring microincinerated preparations the sites occupied by the intracellular neurofibrils are free from mineral ash, the cytoplasmic ash of normal cells corresponding exclusively to the Nissl bodies (fig. 21, second cell from the left). Faulty staining in any of these cases may fail to show the intracellular neurofibrils; such specimens are immediately recognizable by their dull, dirty brown color; under a higher magnification the nuclei are seen to be stained uniformly black, similar to their appearance in the "soaking change" (Alexander [3]); the cytoplasm, however, is stained homogeneously pale brown or purple, with a few spots of irregular, granulated appearance and with a few impregnated, brown-blackish crumbs and rods along the edges of the cell, with, however, no continuous impregnated strands (fig. 23*B*). If the stain is repeated on neighboring sections, normal neurofibrillar impregnation can be effected in all these instances of mere staining artefacts.

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28. Hechst, B.: Zur Histochemie und Histogenese der senilen Plaques, in Schaffer, K.: Hirnpathologische Beiträge, Budapest, Hungary, 1930.

29. Winkler-Junius, E.: Die Bedeutung der Mikroglia für die Entstehung der senilen Plaques, Ztschr. f. d. ges. Neurol. u. Psychiat. **144**:276, 1933.

In 3 cases an alteration in the neurofibrillar picture was observed, which has been described by one of us [3] as a "soaking change." It was seen in 2 cases of cerebral edema (cases 18 and 21) and in 1 case of cerebral atrophy (case 17); the time of autopsy after death in these cases was two, nine and twenty-nine and three-fourths hours, respectively, with an average of thirteen and one-half hours. This change consisted in the appearance of dark-stained, highly argyrophlic granules, crumbs and rods, from 0.52 to 2.08 microns in diameter, in the cytoplasm of the affected cells, with (fig. 22 *A* and *B*) or without (fig. 22 *C*) normal neurofibrils being visible in the same cells, and in the appearance of highly argyrophilic, black-stained marginal rods and strands, measuring from 0.78 to 2.6 microns in thickness, most of them of a somewhat irregular, granular outline, in cells apparently devoid of normal neurofibrils (figs. 22 *D* and 23 *C*). This change is not a staining artefact, since repeated staining of neighboring sections will consistently produce the same picture, and in less severely affected areas normal neurofibrillar impregnation may be seen in neighboring normal cells. However, the hyperargyrophilic granules, rods and strands do not follow the same staining rules as normal neurofibrils, because they are equally well, almost better, seen in preparations subjected to the type of faulty staining already described, which fails to stain the intracellular neurofibrils of neighboring normal cells but stains their cytoplasm homogeneously pale. The same is true also of the hyperargyrophilic strands characteristic of Alzheimer's cell disease, as will be discussed later.

Microincinerated sections from tissue exhibiting the "soaking change" show that in the affected ganglion cells the ash picture is severely altered; the globular arrangement of the cytoplasmic mineral ashes is lost; these cytoplasmic ashes, however, are arranged along the margins of the cells in strands composed of granules and rods, which correspond in their arrangement to the marginal overargyrophilic strands of neighboring Bielschowsky preparations (fig. 22 *E*; compare with 22 *D*). This shows that the "soaking change" is recognizable also in microincinerated preparations, as a shift of the heat-resistant cell minerals from the Nissl bodies into the interglobular spaces normally occupied by neurofibrils, especially toward the margins of the cytoplasm. In some instances, also, the nuclei appear loaded with mineral (fig. 22 *E*), which is normally absent, explaining the increased argyrophilia of nuclei in Bielschowsky preparations (fig. 22 *D*). Another similarity between the overargyrophilic granules, rods and strands seen in the "soaking change" in Bielschowsky preparations and the mineral ash is that long fixation in formaldehyde lessens both the degree of argyrophilia of these structures and the brilliancy of the ash residue (Alexander and Wu,[16] page 83; Alexander and Myerson,[23] page 409).

We are inclined, therefore, to consider the "soaking change" as due to disarrangement of the heat-resistant cell minerals, a change which in all probability takes place after death, at least to its full extent, but which is conditioned in its development by antemortem edema or dehydration. This does not exclude the fact that in some cases it may actually develop before death, during long cachexia or agony. However, we have not yet encountered definite proof.

The next type of neurofibrillar alteration is that seen in ganglion cell disease of pellagral type. In case 30, one of chronic alcoholic paranoid psychosis with partial Korsakoff symptoms and severe polyneuritis (complicated by poisoning with Jamaica ginger [triorthocresyl phosphate]), four and one-half hours post mortem the large ganglion cells of various cortical regions (e. g., areas entorhinalis, centralis and frontalis granularis) showed swelling with central tigrolysis, such as is observed in axonal reaction and, notably, in pellagral cell disease (Parhon and Papinian,[11] Marinesco [30] and Rezza [13]). In Bielschowsky preparations the swollen cytoplasm of the ganglion cells showed a honeycombed network, the silver-stained meshes of which were thicker, coarser and somewhat more argyrophilic than normal neurofibrils and measured 0.78 micron in thickness (fig. 16 *A*); they accumulated along the edges of the cells. No doubt is expressed in the literature that the threads of this network are thickened or massed neurofibrils; we also believe that this interpretation can be accepted. The nuclei of some of the cells showed dark impregnation. Neighboring microincinerated preparations revealed that the heat-resistant cytoplasmic ashes were exclusively contained in the threads of the honeycombed network which were so heavily impregnated in Bielschowsky preparations, while the sites corresponding to the Nissl bodies, in contrast to normal cells, did not show any ash residue (fig. 16 *B*). This is especially well illustrated in figure 21, which shows three cells from the area entorhinalis in the same case. The two cells to the left are normal, especially the second cell from the left, which exhibits the characteristic normal arrangement of the heat-resistant cell minerals in the Nissl bodies of the normal ganglion cell, while the interglobular spaces, which are normally occupied by the intracellular neurofibrils, are free from ash residue. The cell to the right is pathologic: It is enlarged, rounded and swollen; the heat-resistant mineral ashes, instead of being in the Nissl bodies, are contained in the interglobular spaces, forming a continuous network; the sites previously occupied by the Nissl bodies are free from ash, except for a few globules here and there, especially along the cell margins. This shows that this cell disease of pellagral or "axonal" type is char-

30. Marinesco, M. G.: Lésions des centres nerveux dans la pellagre, Compt. rend. Soc. de biol. **51**:919, 1899.

acterized by a shift of the heat-resistant cell minerals from the Nissl bodies into the interglobular spaces, which are normally occupied by the intracellular neurofibrils; this addition of mineral to the interglobular tissue is accompanied by increased argyrophilia of the neurofibrillar network contained in these interglobular spaces. We have seen and followed this shift of the heat-resistant cell minerals in a similar cell disease which one of us (L. A.) and his associates (Alexander and Patton [31] and Alexander and Myerson [23]) were able to produce in cats by experimental dehydration induced by repeated injections of salyrgan and a 50 per cent solution of urea. The material contained between the meshes of the honeycombed network does not stain with silver or aniline dyes; in some instances it consists partly of lipoid and neutral fat.

A similar, but slighter, change, consisting of increased coarseness of the neurofibrils, which were thickened up to 0.78 micron and formed honeycombed networks, but with densely woven meshes, was seen in 3 cases: in case 9, of cerebral atrophy (pseudoatrophy) associated with pulmonary and intestinal tuberculosis and severe emaciation in a woman aged 35 with schizophrenia, on whom autopsy was performed two hours after death; in case 15, of cerebral atrophy in a patient with Korsakoff's psychosis complicating chronic alcoholism, on whom autopsy was performed nineteen and one-half hours after death, and in case 27, of convolutional atrophy with hydrocephalus internus associated with congenital spastic diplegia and mental deficiency, in which the patient died of intestinal obstruction and in which autopsy was performed seven and one-half hours after death.

In the case of Alzheimer's disease (case 28), the typical thick hyperargyrophilic strands of smooth, even outline, measuring from 2.6 to 3.68 microns in diameter, were seen two hours post mortem, most of them in cells devoid of normal neurofibrils (figs. 16 *C* and *D;* 17 *A, B, C, D* and *E;* 18 *A,* and 20 *B*), while neighboring normal cells showed a normal neurofibrillar pattern (fig. 19 *D*). The shape of the Alzheimer strands was that of straight or conic spikes (figs. 17 *A, B* and *C* and 19 *B*), waves (fig. 16 *D*), spirals (fig. 16 *C* and 17 *E*), loops (fig. 17 *D*), whorls (fig. 20 *B*) or more or less winding strands (figs. 17 *C,* 18 *A,* 19 *C* and *D* and 20 *A*). These strands were homogeneous in most cells, while in some they showed striation reminiscent in arrangement and width of that of normal neurofibrils (figs. 17 *B* and *E* and 19 *C*). In some instances of less severely affected cells, Alzheimer strands and normal neurofibrils could be seen side by side in the same cell (fig. 19 *A* and *B*). This observation was first made by Bielschowsky,[32] who concluded

31. Alexander, L., and Patton, W. E.: An Experimental Study of Neurological and Neuropathological Sequelae of Dehydration, to be published.

32. Bielschowsky, M.: Zur Kenntnis der Alzheimerschen Krankheit (präsenilen Demenz mit Herdsymptomen), J. f. Psychol. u. Neurol. **18**:273, 1911; Beiträge zur Histopathologie der Ganglienzelle, ibid. **18**:513, 1912.

from it and from the observation of strands with fine "neurofibrillar" striation that Alzheimer's strands are the result of impregnation of neurofibrillar structures with a foreign substance or substances.

The staining conditions of the Alzheimer strands and those of normal neurofibrils are different, the Alzheimer strands staining more readily and easily than normal neurofibrils and being unaffected by a number of subtle factors and faults that interfere with the proper impregnation of normal neurofibrils. In preparations which show faulty staining characterized by homogeneous, pale appearance of the normal cytoplasm and by dark, homogeneous overstaining of all nuclei, Alzheimer strands contained in neighboring cells (fig. 20 *A*) or in a part of the same cell (fig. 20 *C*) stain just as well as, or sometimes better, blacker and in greater contrast than, in correctly stained preparations. In this respect, namely, in their staining properties, the Alzheimer strands have a great deal in common with the strands and rods of the "soaking change"; their main difference is that of shape, most of the latter being more irregular and uneven. In microincinerated preparations the Alzheimer strands stand out as hypermineralized (fig. 18 *B*), in contrast to normal neurofibrils, which are free from mineral ash; this confirms the previous observation of Alexander and Myerson.[23]

In the case of Pick's disease (case 6), sixteen hours post mortem, the shrunken ganglion cells, which in Nissl preparations showed a dustlike granular pattern of the cytoplasm, corkscrew deformity of the apical processes and shrinkage and folding of the nuclear membrane (fig. 3 *A*), in Bielschowsky preparations showed either a honeycombed neurofibrillar pattern, the meshes of which were thickened (0.78 micron in diameter) and slightly hyperargyrophilic (fig. 10 *A*) or thickened, hyperargyrophilic rods and marginal strands of irregular, uneven outline (figs. 3 *B* and 4 *C*), measuring up to 2.6 microns in thickness; most of them, however, were from 0.78 to 1.04 microns in diameter. In neighboring microincinerated preparations these nets, rods and marginal strands were seen to contain ample ash residue (fig. 10 *B*), in contrast to normal neurofibrils, which were free from mineral ash. The swollen cells, in Nissl preparations, showed a finely granular cytoplasm which, except for the sparse granules, was pale (fig. 4 *A*), while the nucleus showed either slightly increased density with basophilic granular material (fig. 4 *A*) or pyknosis and was displaced toward the edge of the cell (fig. 5 *A*). In Bielschowsky preparations the swollen cells showed hyperargyrophilic marginal rods, globules and thick strands of a somewhat irregular granulated appearance, while the center was taken up either by a fine honeycombed network, the meshes of which measured from 0.52 to 0.78 micron in thickness (fig. 4 *B* and *D*) or was homogeneously pale (fig. 5 *B*). In neighboring microincinerated prepara-

tions the marginal rods and strands of the swollen ganglion cells were seen to be hypermineralized, leaving a heavy ash residue (fig. 5 *C*).

(*c*) *Observations Concerning the Special Histopathologic Changes in Pick's Focal Senile Atrophy.*—In addition to the pathologic changes in the ganglion cells in Pick's disease, which has been dealt with in the preceding section, a few points deserve brief emphasis beyond their description in the complete protocol (see pages 1079; 1083-1092). One of these is the dense and intensive astrocytic and oligodendroglial gliosis in the white matter (fig. 2). This gliosis, which was most intensive along the borders between the gray and the white matter (fig. 1 *A*) and was characterized by hypermineralization (figs. 1 *C* and 11), must, owing to the nature of the disease, be considered as definitely secondary or reparative, not as primary or blastomatous. Similar glioses with hypermineralization were seen in scars following experimental lesions (Alexander and Campbell [33]) and in certain scars following incomplete circulatory infarcts. In most circulatory infarcts, however, the gliosis is not intensive enough to cause hypermineralization, and the same is true of the plaques of multiple sclerosis (Alexander and Myerson [23]).

Another point is the observation of vascular changes, consisting of thickening and hyalinization of the walls of intracerebral blood vessels in the white and gray matter, including large, middle-sized and small arterioles and capillaries (figs. 6 and 7). However, no instances of complete occlusion or thrombosis were seen.

A third point is the fact that the ash picture in this case was correlated with the glial architecture rather than with the myeloarchitecture (compare figs. 1 *A, B* and *C* and 11). Areas of demyelination (fig. 1 *B*) may fail to show demineralization or may even show hypermineralization, wherever the gliosis was very intensive (fig. 1 *C*).

SUMMARY

1. The main object of this investigation was the study of the hyperargyrophilic structures observed in senile psychoses with dementia and of those occurring in other conditions with a method adapted to disclose part of their fundamental chemical composition. The method is that of microincineration, which, though unable to differentiate specific chemical entities (apart from iron, calcium and silica), demonstrates the total heat-resistant mineral ashes in their original topographic arrangement within the tissue.

2. Neurofibrillar structures which appear thickened, massed and hyperargyrophilic when examined by silver impregnation (Bielschowsky stain) appear hypermineralized in corresponding microincinerated prep-

33. Alexander, L., and Campbell, A. C. P.: Local Anaphylactic Lesions of the Brain in Guinea Pigs, Am. J. Path. **13**:229 (March) 1937.

arations. This applies equally to the intracellular strands, rods, globules, granules and nets characteristic of Alzheimer's ganglion cell disease, Pick's disease, pellagral ganglion cell disease and the "soaking change." Normal intracellular neurofibrils are free from ash residue.

3. Senile plaques are localized metaplasias of the glial reticulum, which, although more densely woven, may be of finer caliber in the plaques than in the surrounding normal tissue. Participation of tissue elements other than the glial reticulum (pyknotic ganglion cells, microglia cells and blood vessels) is incidental.

The observation of neither an increase nor a decrease of ash residue at the sites of senile plaques (Alexander and Myerson [23]) is confirmed.

4. The gliosis (astrocytic and oligodendroglial) in the white matter in Pick's disease is so intensive as to cause hypermineralization of the affected areas.

5. The intracerebral arterioles and capillaries in Pick's disease show thickening and hyalinization of their walls, although there is no occlusion.

DISSEMINATED ENCEPHALOMYELITIS (MENINGO-ENCEPHALOMYELORADICULITIS) VERSUS MULTIPLE SCLEROSIS

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Disseminated lesions of the central nervous system may be inflammatory (encephalomyelitis), acute or subacute degenerative (multiple degenerative softening), chronic degenerative (multiple sclerosis) and neoplastic (multiple tumors). Of the aforementioned, the best studied is the chronic degenerative form known as multiple sclerosis. Disseminated inflammatory (nonsyphilitic) lesions are less known; subacute degenerative lesions (multiple degenerative softening) are commonly referred to as acute or malignant multiple sclerosis, while disseminated cerebrospinal tumors are exceptionally rare and, for this reason, are not considered in the differential clinical diagnosis. Disregarding for the moment the last type, I shall record here my observations on the disseminated inflammatory type of lesions of the central nervous system and contrast them with the changes occurring in multiple sclerosis and multiple degenerative softening.

REPORT OF A CASE

A white woman aged 43 was admitted to the Research and Educational Hospitals on July 16, 1936, because of paralysis of the lower extremities and genitourinary disturbances. She died the next day.

History.—The patient's father died at the age of 57 of "heart disease," and a sister died of "paralysis"; the mother, 4 brothers and another sister were all living and well. The patient, who had always been sickly, had had scarlet fever, streptococcic sore throat, measles, whooping cough, mumps and chickenpox. She denied having had venereal disease, miscarriages or abortions, but had always complained of innumerable aches and pains.

The present illness dated back forty-five days, when her right foot "kicked out" while she was walking on the street. The "kicking out" did not interfere much with the gait, and the patient returned safely home, after having walked 4 miles (6.4 kilometers). She stayed in bed two weeks, and one week later began to experience sensations of pins and needles in the right thigh and leg, which

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commenced to "kick" again. This time the salivary glands, urinary bladder and intestines "stopped functioning."

Examination.—The patient was paralyzed in the lower extremities and was apathetic and slow in responding. The pulse and temperature were normal. The right pupil was smaller than the left (4 and 5 mm., respectively); the right palpebral fissure was somewhat narrower than the left, though there was no definite ptosis; the corneal reflexes were present, and a questionable hypalgesia was present on the right half of the forehead; the lower part of the left facial nerve showed slight weakness. A note made during examination in another hospital (July 9, 1936) mentioned "temporary" paresthesia and numbness in the left side of the face. The tendon reflexes were all present bilaterally; no pathologic reflexes were elicited. Below the fifth thoracic segment there was complete anesthesia, which was bordered by a zone of paresthesia corresponding to the third and fourth thoracic segments. Speech was nasal; the neck was slightly rigid, and there was retention of urine and feces. There was no athetosis, tremor or other signs of involvement of the basal ganglia.

Laboratory Data.—Examination of the blood revealed: white cells, 21,000, 89 per cent of which were polymorphonuclears; red cells, 4,200,000; dextrose, 140 mg. per hundred cubic centimeters, and nonprotein nitrogen, 64 mg. The spinal fluid contained 450 cells (polymorphonuclears) per cubic millimeter; there were 69 mg. of total proteins per hundred cubic centimeters, 686 mg. of chlorides and 52 mg. of sugar; globulin was present (1 plus). The urine contanied albumin (3 plus).

Examination on July 9, in another hospital showed that the spinal fluid was clear and contained 10 cells per cubic millimeter. The Ross-Jones and Pandy reactions were faintly positive. The Wassermann test was made elsewhere and gave a negative reaction.

Course.—During the patient's one day in the hospital, swallowing became difficult; speech became indistinct; the anesthesia rapidly extended upward to the first thoracic segment; a Babinski sign could be elicited on both sides; the reflexes all disappeared, and involuntary urination set in. The temperature continued to rise until death.

Summary of Clinical Findings.—The significant clinical findings were: motor restlessness ("kicking") in the lower extremities, followed by paralysis; paresthesias and anesthesia of the body, which gradually extended upward to the first thoracic segment; a mild Horner syndrome on the right, with ipsilateral hypesthesia in the area of the upper branch of the fifth nerve; paralysis of the bladder and rectum; normal tendon reflexes, which later became abolished; weakness of the lower part of the left facial nerve and rapid development of bulbar symptoms; a high temperature, and death within forty-five days after the onset.

A diagnosis of encephalomyelitis was made.

Observations at Necropsy.—The main observations were: hypostatic bronchopneumonia involving the lower lobes of both lungs; parenchymatous degeneration of the liver, kidneys and heart, and catarrhal cystitis.

The brain exhibited somewhat enlarged and flattened convolutions, transparent and otherwise normal meninges with normal arteries at the base and normal size of the cerebral ventricles. There was absence of tumors, hemorrhages or macroscopic foci of softening.

Microscopic Observations.—Spinal Cord: No gross changes, such as areas of demyelinization, were present in sections stained by the Weigert-Pal method. Sections from the cervical and lumbar areas stained with toluidine blue exhibited occasionally mild infiltrations of the white substance and the meninges. In the midthoracic region, however, the infiltrations were immense, especially in the posterior columns along the posterior septum and the posterior commissure. The infiltrating cells were all lymphocytes and, as a rule, were confined to the Virchow-Robin adventitial spaces. Only in few instances did the infiltrating cells invade

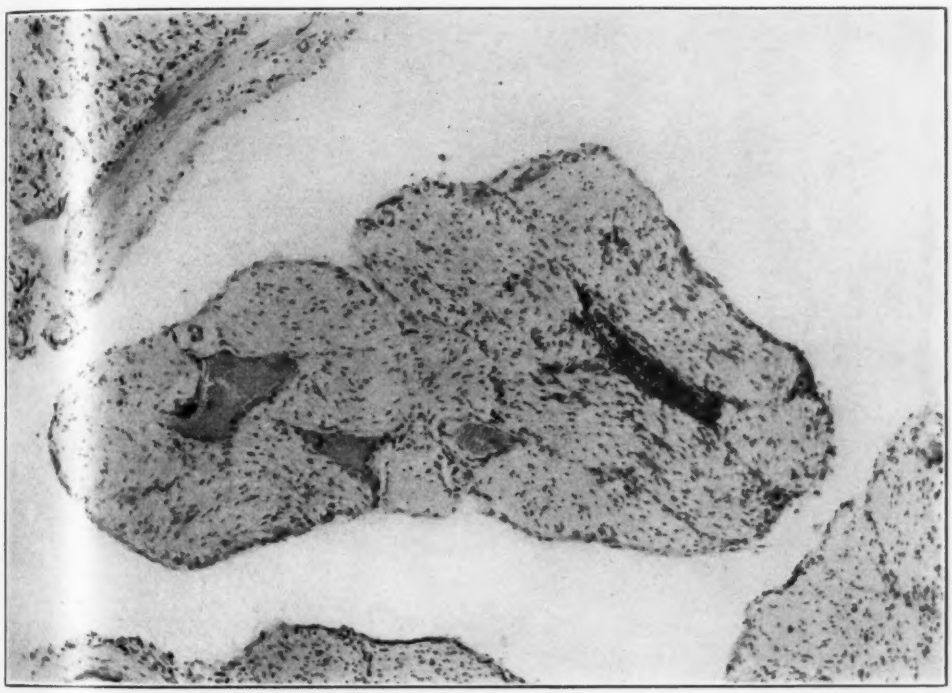

Fig. 1.—Posterior roots of the spinal cord. The part of the root in the center shows a densely infiltrated blood vessel.

the surrounding parenchyma. The infiltrations were occasionally so dense that they affected the size of the vascular lumen, which they often obliterated. Only in mildly infiltrated blood vessels was it possible to differentiate arterioles and venules and to determine the condition of the endothelial and adventitial cells of the vascular walls, which in the spinal vessels were normal. The veins were not infiltrated more than the arteries, and the infiltrating cells were almost always lymphocytes, without admixture of polymorphonuclear and gitter cells. The infiltrating cells did not form nodules, nor were there signs of proliferation of the intima or formation of tubercles or gummas. The changes outlined were also present in the anterior and posterior spinal roots and the meninges (fig. 1).

More widespread were the parenchymatous changes in the spinal cord. Mild in the cervical and lumbar regions, where such changes appeared as slight tumefaction of the ganglion cells combined with satellitosis, they were much more marked in the midthoracic region. Here the cell changes varied from tumefaction to liquefaction and intense neuronophagia, when the ganglion cells were often transformed into a shapeless mass invaded by neuronophages. In such foci the glia cells appeared as homogeneous pale cytoplasm without processes, but with an eccentric pyknotic nucleus (ameboid glia cells, figs 2 *Am* and 3), and the glia fibers broken up into Alzheimer's filling bodies (Cajal's clasmatodendrosis, figs. 2 and 3 *F*). In the adjacent less affected areas gitter cells and even stray astrocytes

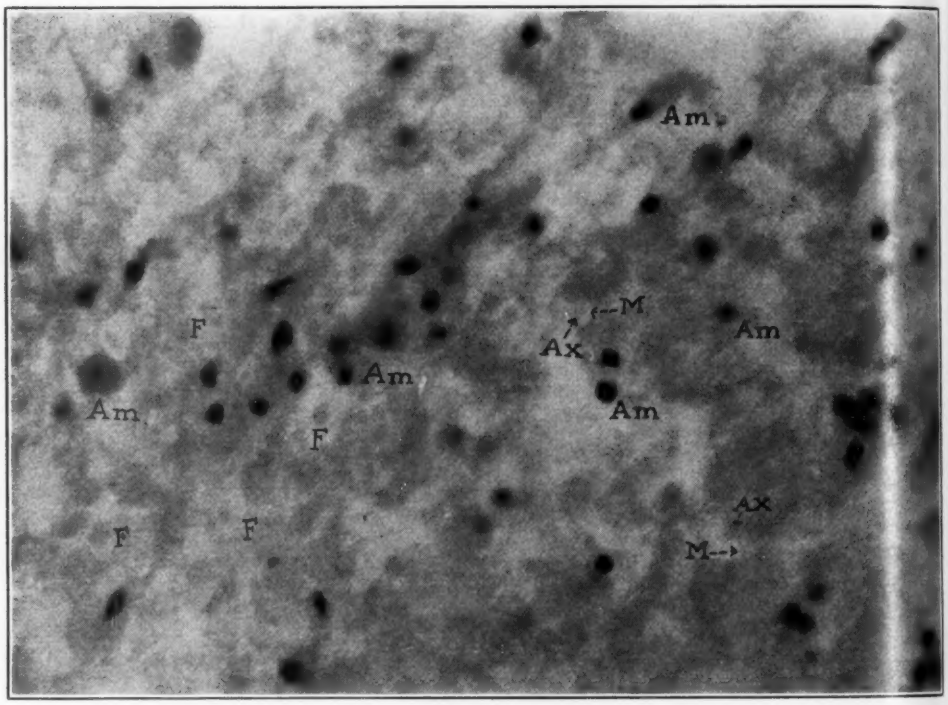

Fig. 2.—*Am* indicates ameboid glia cells; *F*, filling bodies; *Ax*, an axon, and *M*, swollen myelin. Both *Am* and *F* are reproduced as drawings in figure 3. Toluidine blue stain.

could be seen. The gitter cells were irregular (fig. 3 *b*); their nuclei were rich in chromatin and were always situated at the periphery; their vacuoles were also irregular; some were minute, others were large but possessed no axon and contained no fragments of myelin and were anchored in the parenchyma. Such cells resembled Jakob's gitter cells —b (figs. 3 and 4) and were intermingled with sausage-like microgliocytes. The latter type of cells could be discerned well in the gray matter of the spinal cord, but more in the white substance, especially in longitudinal sections (figs. 5 and 3 *m*), in which they appeared as rod cells with branching processes emanating from their poles and running parallel to the white nerve fibers. In some instances it was possible even to trace transformation

of the branching processes into vacuoles and gitter cells of the aforedescribed variety (Jakob's type —b). Typical gitter cells (the g variety of Jakob, figs. 3 and 4*g* and *G*), round mobile elements (with the vacuoles minute but uniform in size and the nucleus at the periphery) irregularly scattered over the parenchyma as if they had broken loose, were uncommon.

Medulla, Midbrain and Diencephalon: The medulla exhibited marked asymmetry (fig. 6). The left half (right in the picture) was considerably larger in both length and width than the right and was demyelinated. Only the pyramids were spared. Similar areas of demyelination were present in the right caudate nucleus

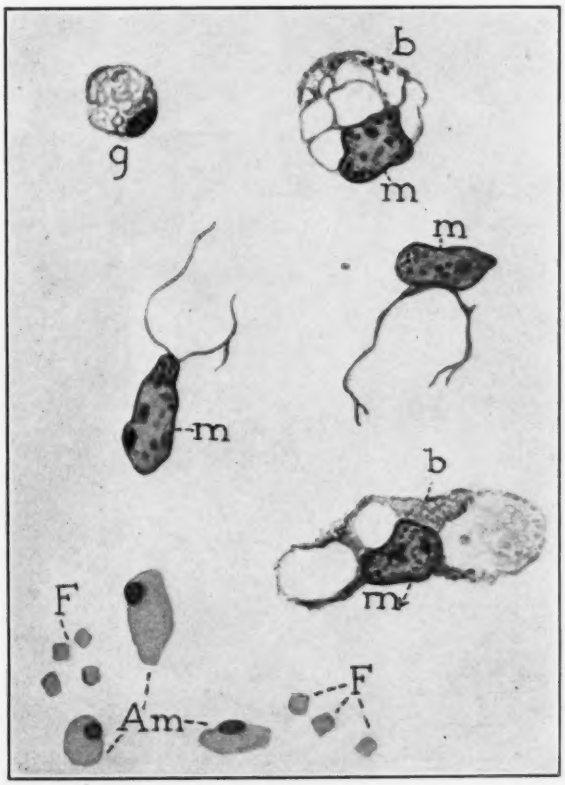

Fig. 3.—Drawings of microglia cells (*m*), gitter cells (*b* and *g*), filling bodies (*F*) and ameboid glia cells (*Am*).

(fig. 7) and the globus pallidus. The impression was that the patches were those of multiple sclerosis, but cell-containing methods revealed the aforementioned areas to be highly cellular. The majority of the cells have already been described: gitter cells —b (figs. 3 and 4) filled with lipoids and mixed with microgliocytes and oligodendrocytes, plasma cells and occasionally cytoplasmic astrocytes, which often fused to form Nissl's *Rasen* and the typical gitter cells, *g*.

The ganglion cells were much changed. They exhibited phenomena of marked satellitosis and neuronophagia, and in the corpus striatum both the large and the small ganglion cells were affected. In general, the changes varied from acute

swelling of the cell body to liquefaction. In the medulla some ganglion cells, especially those of the olives, resembled the ganglion cells seen in amaurotic family idiocy. The Nissl bodies were lacking; the cell body was tumefied and transformed into a honeycombed structure; it was devoid of dendrites, and the

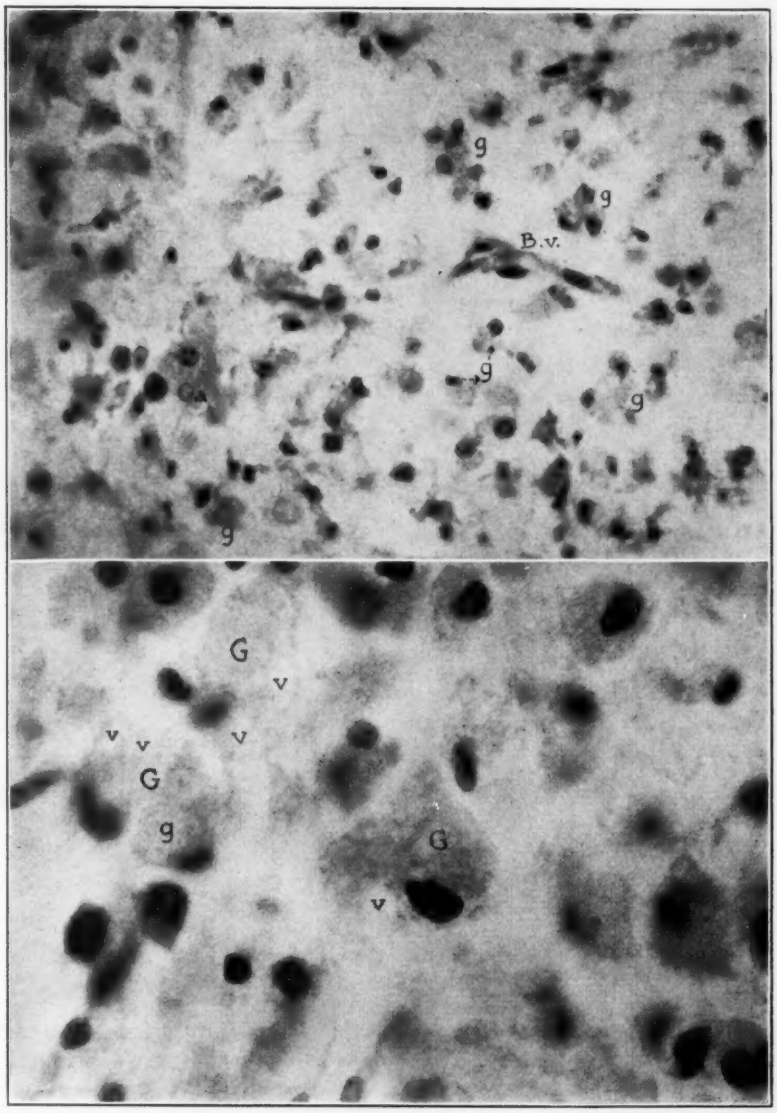

Fig. 4.—These photomicrographs represent the principal cells of a degenerated area. Some of the cells of enormous size are reproduced in the lower portion, under a higher magnification. *Ga* indicates a ganglion cell; *g* and *G*, gitter cells; *B.v.*, a blood vessel, and *v*. vacuoles. Toluidine blue stain.

nucleus was well supplied with chromatin and displaced to the periphery, protruding into the axon. Much as the ganglion cells were changed, the changes in the white substance were even more striking. Thus, in the right corpus striatum the anterior limb of the internal capsule was for the most part degenerated; only a small portion remained undamaged; the corresponding globus pallidus showed hardly any preserved white fibers; in the medulla oblongata the retro-olivary area and the olivary body itself exhibited marked degeneration on the left (on the right in fig. 6). Only the pyramids and some transverse fibers in the left upper half were preserved, but the degenerated focus protruded into the right half of the medulla (left in picture), forming a distinct curve. Sections stained by the method of Bielschowsky showed few axons; like the toluidine blue stains, these

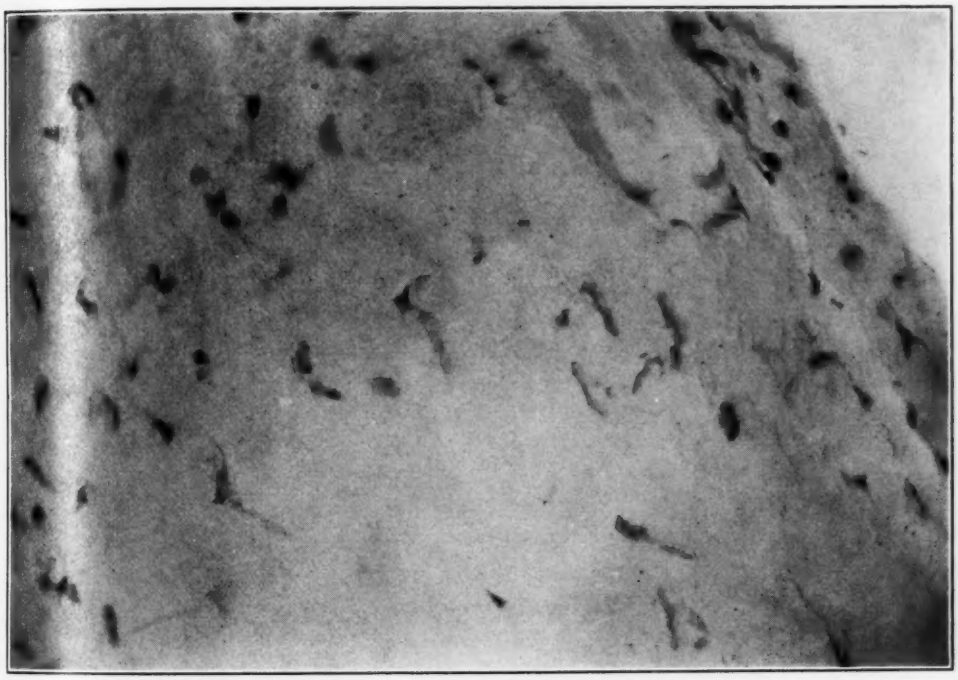

Fig. 5.—Microgliocytes in longitudinal sections of the spinal cord. Toluidine blue stain.

preparations revealed extensive changes in the ganglion cells and enormous infiltrations (fig. 6) of the blood vessels. As in the spinal cord, the infiltrating cells of the blood vessels of the bulb were all lymphocytes; in the globus pallidus and corpus striatum these cells were mixed with a few gitter cells and plasmocytes, which usually were large; the smaller blood vessels, including the capillaries, were also infiltrated and occasionally showed proliferation of the endothelial cells and thrombi. The large blood vessels of the base (the basilar and the vertebral artery and its branches) did not exhibit such changes as infiltrations, thickening or proliferation of the intima, formation of tubercles, gummas or thrombi or splitting of the elastic tunic. Small agonal hemorrhages were occasionally encountered in the medulla and globus pallidus.

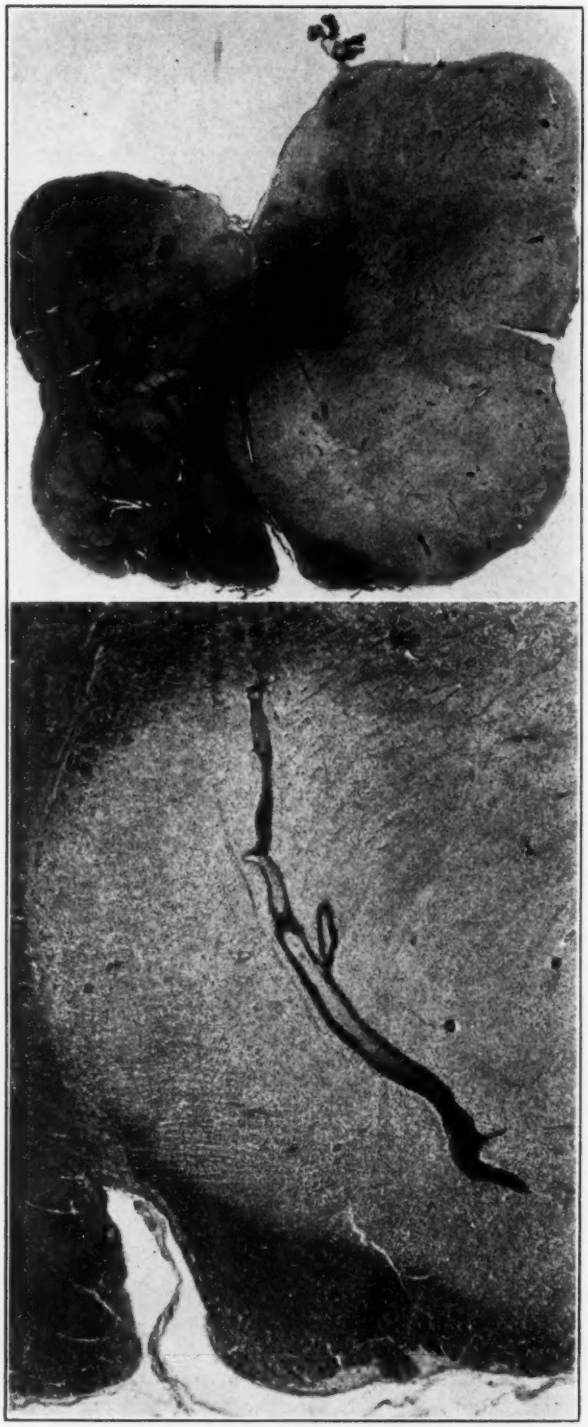

Fig. 6.—The left half of the medulla (to the right of the picture) is demyelinated; it is asymmetric, considerably larger than the opposite, well stained half and shows numerous densely infiltrated blood vessels in the upper part of the picture. The lower half of the picture, taken with a high power lens, is from a different level and shows the dense infiltrations obliterating some portions of the blood vessel and demyelination. Van Gieson stain.

The regions of the brain stem which escaped marked degeneration were by no means normal. Thus, the right half of the medulla also contained infiltrated blood vessels, but these were less numerous; the microglial reaction was marked, and parenchymatous changes (satellitosis and neuronophagia) were common. Similar changes were present in the optic thalamus and pons, but were absent in the substantia nigra, corpus callosum, optic nerves and walls of the cerebral ventricles. No spirochetes were observed in the parenchyma or the infiltrated blood vessels.

Cortex and Cerebellum: The frontal, parietal and occipital lobes and the cerebellum were normal. Only in the cornu ammonis were inflammatory and degenerative changes observed in the form of mild perivascular infiltrations and slight neuronophagia.

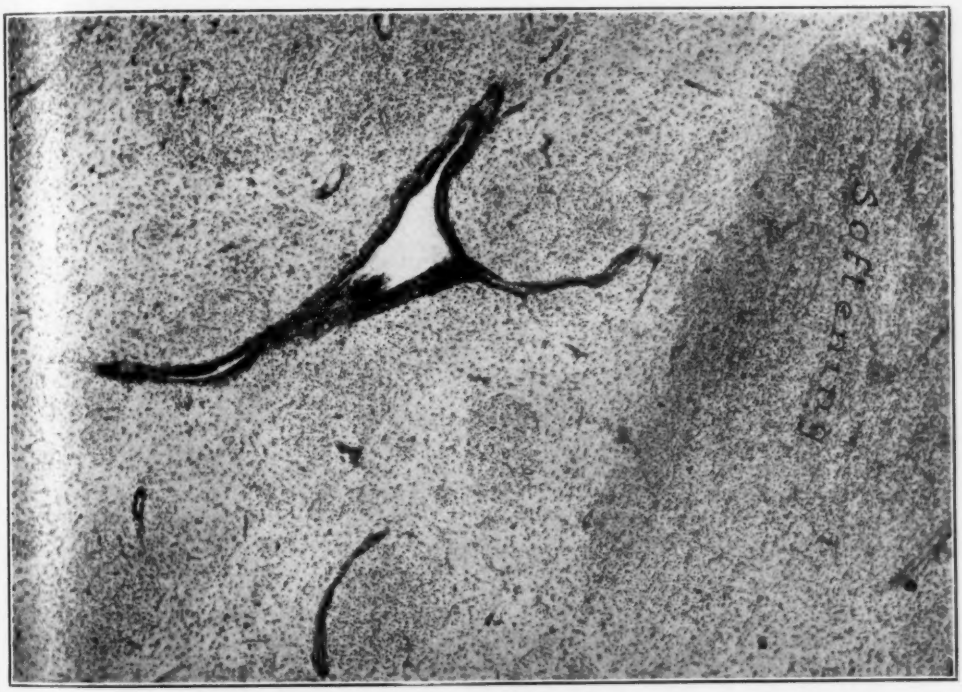

Fig. 7.—Photomicrograph of the corpus striatum, showing the intense infiltration of the blood vessels, large and small, combined with extensive areas of softening.

Cerebral Meninges and the Subarachnoid Space: The pia-arachnoid and the dura exhibited vascular lymphocytic infiltrations, mainly perivenous, which in their features resembled those of the spinal cord. The subarachnoid space was distended and contained lymphocytes and plasma cells; the arachnoid membrane, cerebral and spinal, showed typical villi with a vast number of proliferated mesothelial cells. The dura and the epidural space of the spinal cord were mildly infiltrated, but the perineurial, endoneurial and subdural spaces were not affected, as they are, for instance, in tabes.

The choroid plexus exhibited marked destruction of the tuft cells.

Summary of Histologic Observations.—There were: infiltrative and parenchymatous changes in the spinal cord (white and gray substances), medulla, pons, basal ganglia (optic thalamus, right corpus striatum and globus pallidus), anterior limb of the right internal capsule and cornu ammonis; mild and inconstant reactive phenomena in the glia, with pronounced changes in the microglia cells and transformation of the latter into Jakob's gitter cells —b, and infiltrative inflammatory changes in the meninges and anterior and posterior roots of the spinal cord. One thus may speak of disseminated meningoencephalomyeloradiculitis.

COMMENT

The changes outlined adequately explain the motor, sensory and genitourinary disturbances, the bulbar signs and the rapidly fatal course. The changes were disseminated throughout the cerebrospinal nervous system, including the meninges and the spinal roots. The vascular phenomena were similar to those occurring in diseases generally considered inflammatory and infiltrative (epidemic encephalitis, epidemic poliomyelitis, Borna disease of horses, African sleeping sickness and rabies), and for this reason should also be classified as inflammatory, as infiltrative encephalomyelitis. As the infiltrations were also present in the meninges and roots, the condition may be classified as meningoencephalomyeloradiculitis. Dense adventitial infiltrations, superficially resembling the aforementioned lesions, may also occur in syphilitic lesions of the brain (dementia paralytica, meningovascular syphilis) and multiple sclerosis. In dementia paralytica the infiltrations and parenchymatous degeneration are mainly in the frontal lobe and affect the cortex, causing its atrophy. In the present case the cortical infiltrations not only were in the cornu ammonis but were exceptionally severe in the basal ganglia, medulla and spinal cord. Such localizations, unusual in dementia paralytica, occur in meningovascular syphilis. Absence of gummas, endarteritis, changes in the elastic tunic, intimal proliferations and involvement of the blood vessels at the base of the brain speak against the changes being due to syphilis.

The inflammatory changes in the present case were associated with vast areas of degeneration (especially in the left side of the medulla, the right corpus striatum and the globus pallidus), which bore a definite relation to certain blood vessels. In the medulla, for instance, the degenerated area coincided with the territory supplied by the left posterior inferior cerebellar, or rather left vertebral, artery. In its extent it was almost identical with a similar demyelinated area pictured by Alexander and Suh [1] (fig. 11 *D*) after injections into the posterior

1. Alexander, L., and Suh, T. H.: Arterial Supply of Lateral Parolivary Area of the Medulla Oblongata in Man, Arch. Neurol. & Psychiat. **38**:1243 (Dec.) 1937.

inferior cerebellar artery. In the nasal ganglia the affected areas corresponded with the territories supplied by the lenticulostriate and lenticulo-optic arteries. Clinical signs of involvement of the aforementioned areas were paradoxic. Thus, the vast degeneration of the left half of the medulla gave no clinical signs of occlusion of the posterior inferior cerebellar artery; however, such signs were present on the opposite side, which was less affected. Nor were clinical pallidal or striatal manifestations in evidence, regardless of the presence of signs of advanced degeneration of the corpus striatum and globus pallidus. Whether the lack of correspondence between the clinical and the pathologic phenomena was due to the lesions, though generally diffuse, being mainly unilateral, the fact remains that degeneration may occur in disseminated encephalomyelitis. This was evidently also present in the cases of Beck [2] and Bouchut and Dechaume [3] (discussed elsewhere [4]). However, degenerative phenomena are to be considered not as an integral feature of this morbid condition but as an accidental complication which makes the course rapid and the prognosis bad. As acute degenerative conditions are incurable and fatal because of bulbar involvement (as in the present case), other complications or grave etiologic factors, it is to be assumed that extensive degenerations, especially when as vast as in the case under discussion, do not occur in ordinary cases of encephalomyelitis, for in such there is usually recovery. The cause of the parenchymatous degeneration may lie in the diseased condition of the arteries or their ramifications within the parenchyma. As figure 6 shows, the infiltration of the branch of the posterior inferior cerebellar artery was immense and obliterated some parts of its lumen. The infiltrations were not only intense but numerous (fig. 6). They involved immense masses of blood vessels and therefore had in some way to affect the parenchyma. The microglial and not glial type of reaction [5] also speaks in favor of a possible vascular factor.

Differentiation from Multiple Sclerosis.—Dense infiltrations may occur even in cases of classic multiple sclerosis (fig. 8). However, analysis under a high power lens or counterstaining with scarlet red will reveal a difference in the types of the elements. Whereas in the present case the infiltration cells were all lymphocytes, mixed in some instances with plasma cells, in multiple sclerosis the infiltrating

2. Beck, G. M.: A Case of Diffuse Myelitis Associated with Optic Neuritis, Brain **50**:687 (Oct.) 1927.

3. Bouchut, L., and Dechaume, J.: Etude histopathologique d'un cas de neuropticomyélite aiguë, Ann. d'anat. path. **4**:357 (Dec.) 1927.

4. Hassin, G. B.: Neuropathic Myelitis Versus Multiple Sclerosis, Arch. Neurol. & Psychiat. **37**:1083 (May) 1937.

5. Hassin, G. B.: Reacting Cells in the Brain in the Presence of a Foreign Body, Arch. Neurol. & Psychiat. **36**:231 (Aug.) 1936.

cells are classic gitter cells (Jakob's g type). Lymphocytes and plasma cells may occur in multiple sclerosis, but only accidentally, and are considered secondary to the presence of gitter cells. In short, the changes in multiple sclerosis are definitely degenerative; in encephalomyelitis they are definitely inflammatory.

As has been repeatedly emphasized, the reactive changes in multiple sclerosis are glial. In the present case they were mesodermal (microglial). Elzholz bodies, myelophages and evidences of successive

Fig. 8.—Multiple sclerosis. The blood vessels are densely infiltrated with gitter cells. Scarlet red and hematoxylin stain.

transformation of broken-up nerve fibers into lipoids, as encountered in multiple sclerosis, were not observed in this case. Here, vast amounts of granules not only were present within gitter cells but were scattered over the visual field as free lipoids, into which the nerve tissue had become transformed by direct action of some toxic-infectious agent. Transformed by such agents into lipoids, the small lipoid granules, like any other débris, were picked up by the microglial histiocytes, which ultimately became transformed into gitter cells (figs. 3 and 4). Toxic factors thus cannot be ignored as an additional probable cause

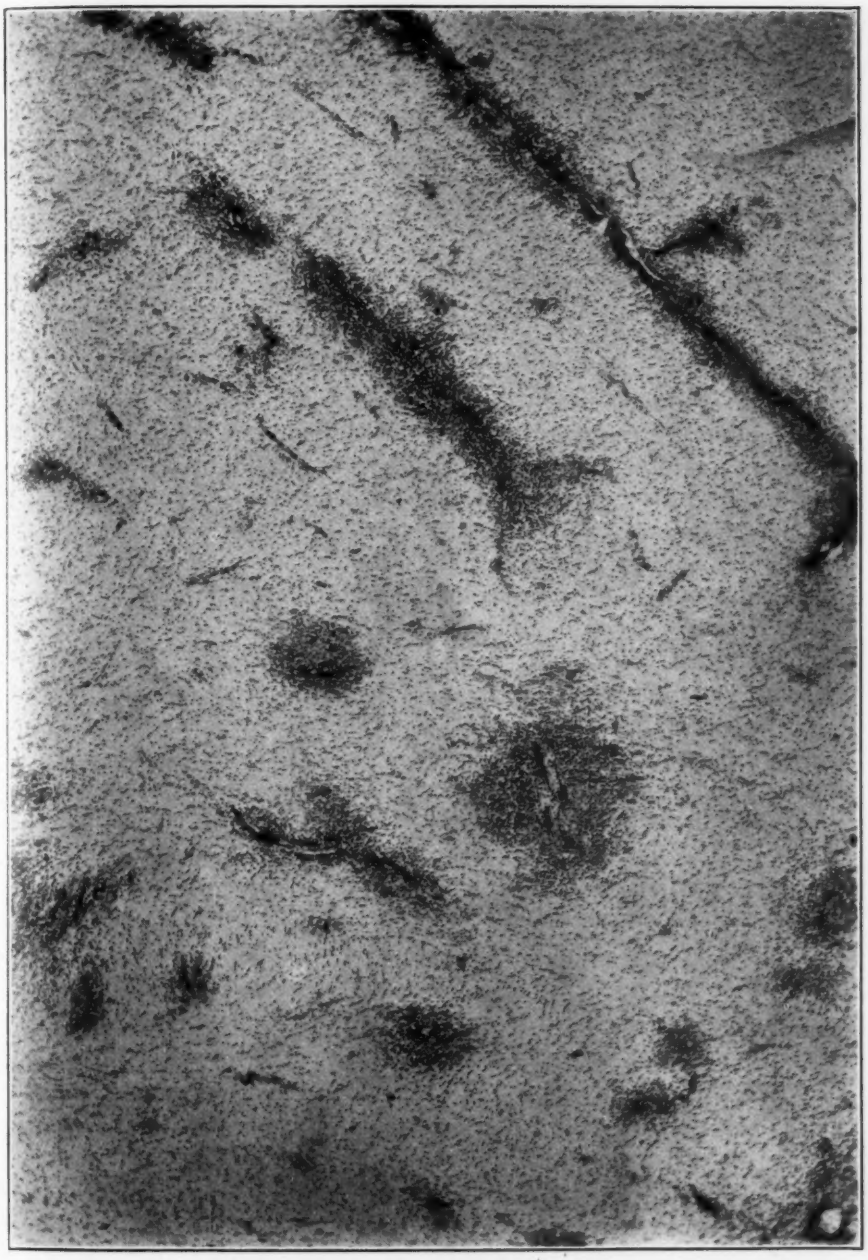

Fig. 9.—Postvaccinal encephalitis. The infiltration of the blood vessels is extra-adventitial. Toluidine blue stain.

of nerve degeneration in this case. In some areas it played an even greater role than the vascular factors. For instance, in the spinal cord the glia itself was badly damaged. It appeared ameboid (figs. 2 and 3) and broken up, which changes are manifestations of severe toxemia, as has been emphasized by Alzheimer.[6] Such glial changes do not occur in multiple sclerosis, in which the outstanding feature is a primary lesion of the nerve fibers, their demyelination accompanied by secondary glial reaction, ultimate formation of foci of sclerosis and absence of primary changes in the ganglion cells.[7] Absence of patches of sclerosis is, of course, the most important difference, for there is no multiple sclerosis without the presence of sclerotic patches, regardless of the clinical age of the disease process. In some pathologic features (patches of demyelination without sclerosis, involvement of both gray and white substances) the present case also resembles those of multiple degenerative softening, with which I include such conditions as neuroptic myelitis,[4] Schilder's disease and septicemias. The predominance in the present case of microglial reaction and lymphocytic infiltrations, which in multiple softening are mixed with gitter cells, the inflammatory involvement of the meninges and roots and the rapid course differentiate the condition from multiple degenerative softening.

It is much easier to differentiate the disease in the present case from another form known as postvaccinal or cowpox encephalitis. Leaving the discussion of this problem for a future contribution, I here wish merely to call attention to the characteristic feature of postvaccinal encephalitis, the extra-adventitial infiltrations, so well shown in figure 9. Multiple sclerosis, infiltrative meningoencephalitis or multiple degenerative softening does not exhibit this type of infiltration. These conditions, nevertheless, are all grouped as one disease process, regardless of the fact that they possess individual pathologic features.

CONCLUSIONS

1. In a case of disseminated meningoencephalomyeloradiculitis of forty-five days' duration, massive hematogenous infiltrations of the blood vessels were associated with scattered foci of nerve degeneration.

2. The occurrence of foci of degeneration in disseminated encephalomyelitis should be considered not as an integral part of the pathologic picture, but as a complication, and only in cases in which the disease runs a fatal course.

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7. Hassin, G. B.: Pathologic Features of Multiple Sclerosis and Allied Conditions, Arch. Neurol. & Psychiat. **38**:713 (Oct.) 1937.

3. There may be a causal relation between the excessive vascular infiltrations and degeneration, but the toxic factor is of greater importance, for changes may be present in areas devoid of infiltrations and vice versa.

4. The reactive changes in the foci of degeneration may be mainly microglial, that is, mesodermal. Such reactive changes do not occur in multiple sclerosis and denote either a vascular factor or severe toxemia as the cause.

5. In the extensive vascular hematogenous infiltrations of the cerebral parenchyma, cord, roots and meninges, encephalomyelitis complicated with foci of degeneration differs not only from multiple sclerosis but also from so-called multiple degenerative softening.

6. Disseminated encephalomyelitis, multiple sclerosis and multiple degenerative softening of the cerebrospinal system are different clinical entities.

PHYSIOPATHOLOGIC AND PATHOANATOMIC ASPECTS OF MAJOR TRIGEMINAL NEURALGIA

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AND
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It has been the general belief and part of the definition of "neuralgia" that in major trigeminal neuralgia no objective sensory disturbance is present. This experience holds true as long as we use pin and cotton wool as means of examination. But when graduated hairs or thorns and the electrical current are applied, we find that in about 25 per cent of our patients with trigeminal neuralgia who have not received any previous treatment the number of touch and pain points is reduced—penesthesia, penalgesia. We also note that the preserved points require a stimulus of greater strength and longer duration to produce a sensation—hypesthesia, hypalgesia. Such quantitative deviations of sensibility of the face are sometimes helpful in judging the operative chance for relief of pain in patients with a combination of typical and atypical features of trifacial neuralgia, as well as in determining the division of the fifth nerve primarily involved. However, when we treat statistically the results of over 900 electrical examinations of the sensibility of the face in 50 patients suffering from major trigeminal neuralgia, it appears that quantitative disturbance of sensibility plays a contributory rather than an essential role in this disease.

In contrast to the aberrant quantitative perception of sensations, qualitative disturbances, or, in neurophysiologic terms, changes in the pattern of sensory impulses, are preeminent in frequency and significance. Summation and radiation, after-effect and hyperpathia, spatial and temporal amalgamation and, finally, complete transmutation of sensations characterize the physiopathologic pattern of sensibility in major trigeminal neuralgia.

Repetitive stimuli of equal strength give rise to pain sensations of increasing intensity, which tend to spread gradually into areas farther from the point of stimulation. The normal correlation between dura-

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tion of stimulus and sensation becomes deranged, and the sensation outlasts the stimulus for seconds or minutes. This phenomenon may mean a delayed decline of excitation—adecremental excitation—or repeated responses to a single stimulus—Sherrington's after-discharge. Both phenomena are closely related to the time factor of excitation. In the first case the refractory period may become so extended that a subsequent stimulus is not perceived at all, or not as a separate excitation. The two stimuli seem to be fused—amalgamation. The appearance of an after-discharge, on the other hand, suggests the formation of a central excitatory state. According to the ruling theory, the central excitatory state is due possibly to depolarization of synaptic membranes. Several subliminal volleys of impulses converge on one synapse; summation occurs, and a central excitatory state is built up. As soon as the threshold is reached, a discharge will occur. The rate of building up the central excitatory state and its inactivation depend on the occurrence of interfering volleys at the same synapse. Corticothalamic inhibitory impulses have been assumed by Head and Holmes [1] to exercise a dampening influence on the pain sensations at the thalamic synapse. What happens when these cortical impulses are abolished is still subject to speculation. However, the results of the recent experiments of Dusser de Barenne and McCulloch [2] seem to throw new light on, and possibly provide a physiologic basis for, the hypothesis of Head and Holmes. In contrast to Sherrington's original conception, it is believed today that a central excitatory state of supraliminal value does not occur.[3] Even so, the discharge may become delayed with pathologic conditions and permit the recruitment of more pain impulses, which eventually discharge with supranormal force. Such a process may be the physiologic correlate of the clinical condition well known in thalamic disease as "explosive pain reactions." There is experimental evidence for the possibility that interference of corticothalamic impulses with the after-discharge of thalamic cells may lead to momentary synchronization of the after-discharge and to its clinical equivalent, paroxysmal intensification of pain sensation. Finally, when the variation of the conduction time in the central pathways further increases, complete transmutation, or, from the point of view of the patient, disorientation, and finally misinterpretation of sensations result.

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1. Head, H., and Holmes, G.: Sensory Disturbances from Cerebral Lesions, Brain **34**:102, 1911.

2. Dusser de Barenne, J. G., and McCulloch, W. S.: Functional Organization in the Sensory Cortex of the Monkey, J. Neurophysiol. **1**:69, 1938; personal communication to the authors.

3. Creed, R. S.; Denny-Brown, D.; Eccles, J. C.; Liddell, G. T., and Sherrington, C. S.: Reflex Activity of the Spinal Cord, New York, Oxford University Press, 1932, p. 44.

The aforementioned anomalies of sensation, such as the "slow response with long after-effects . . . the high threshold of stimuli and the tendency to explosive reactions . . . and the excessive feeling tone of sensations" (Head and Holmes [1]), have been recognized as characteristic signs of a thalamic lesion since Roussy's [4] classic description of the *syndrome thalamique*. In 32 per cent of our patients with trigeminal neuralgia these signs were not confined to the face but extended over one side of the body. In addition, 40 of our 50 patients showed some signs of pyramidal or extrapyramidal involvement. The aggregation of the sensory disturbances already described plus the motor

Fig. 1.—Mrs. G. Typical trigeminal neuralgia on the left. Old softening in the internal and lateral thalamic nuclei bilaterally.

signs and symptoms pointed to the region of the optic thalamus as the possible site of a lesion in major trigeminal neuralgia.

Macroscopic inspection of the brain in 6 cases and histologic investigation of serial sections confirmed this assumption. On the surface of the brain atrophy of the most inferior portion of the postcentral, precentral and frontal convolutions was observed. The postcentral convolution appeared flat and sunken. This atrophy was still more impressive in a cross section of the whole brain. Here we saw that the atrophy of the cortex was negligible in comparison with that of the white matter, which had decreased a full centimeter in width and had retracted, with widening of the lateral ventricle. What is the origin of this loss of nerve tissue? There are two possibilities. The one is

4. Roussy, G.: La. couche optique (étude anatomique, physiologique et clinique); le syndrome thalamique, Thesis, Paris, no. 165, Paris, G. Steinheil, 1907.

exemplified by figure 1, showing bilateral softening in the internal and lateral thalamic nuclei. In spite of the bilaterality of the foci, the trigeminal neuralgia was unilateral at the time of operation. The second form of degeneration, which was prevalent in our small group of 6 brains studied at autopsy, showed a vascular lesion in the corona radiata (fig. 2). This interruption of the thalamocortical fibers led to secondary degeneration toward the cortex and to retrograde degeneration in some nuclei of the optic thalamus, the cells of which gave rise to the destroyed nerve fibers. Consequently, the cortical cells were

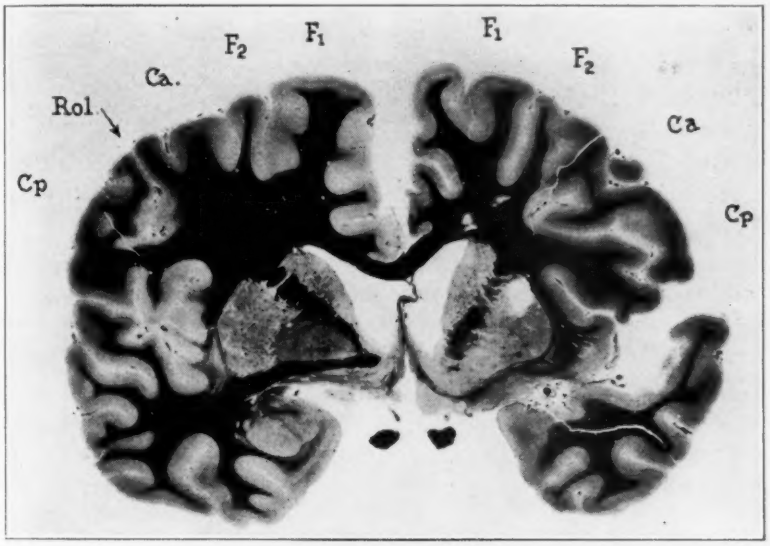

Fig. 2.—Mrs. C. Typical trigeminal neuralgia on the right. The whole right hemisphere, especially the anterior part, is shrunken. The diminution in volume of the white matter is due to the thrombosis and softening in the thalamocortical tract. There is cortical atrophy. *F* indicates the frontal convolution; *Ca*, the anterior convolution; *Cp* the posterior convolution, and *Rol*, Rolando's fissure.

well preserved in general, while the inflowing myelinated fibers were completely absent. In the optic thalamus, on the other hand, Flechsig's arcuate (semilunar) nucleus and Luys's *centre médian* had completely disappeared (fig. 3). The ventral portions of the lateral and the internal thalamic nucleus were considerably smaller on the side of the vascular lesion.

Here we met our second surprise. In all 5 cases in which there was a unilateral lesion the focus was on the side of the trigeminal neuralgia. This, of course, does not conform to the general rules of neurophysiology. We have no autopsy material with a contralateral lesion, nor have we other evidence on this point. In fact, we availed

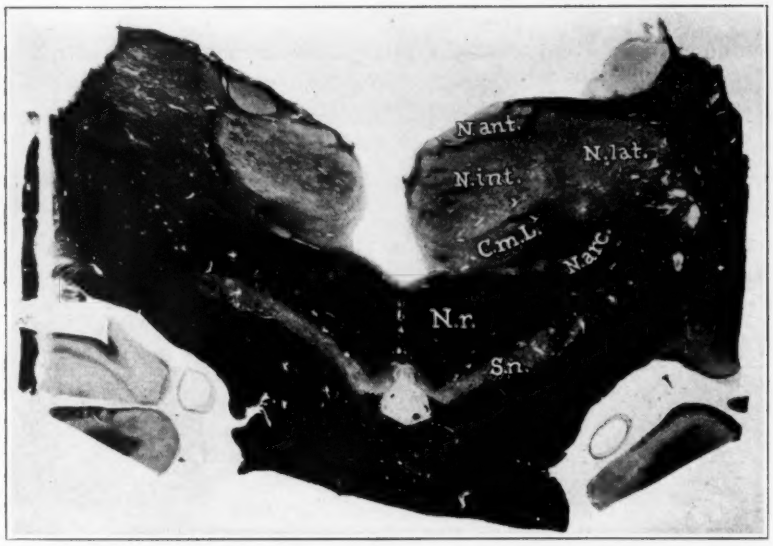

Fig. 3.—Mr. A. Typical trigeminal neuralgia on the left. There are softening in the left thalamocortical tract, complete retrograde degeneration of the left arcuate nucleus and the *centre médian* of Luys and partial atrophy of the lateral thalamic nucleus. The reduction in the internal thalamic nucleus is not visible at this level. *N. ant.* indicates the anterior thalamic nucleus; *N. arc.*, the arcuate (semilunar) nucleus; *N. int.*, the internal thalamic nucleus; *N. lat.*, the lateral thalamic nucleus; *N. r.*, the red nucleus, and *S. n.*, the substantia nigra.

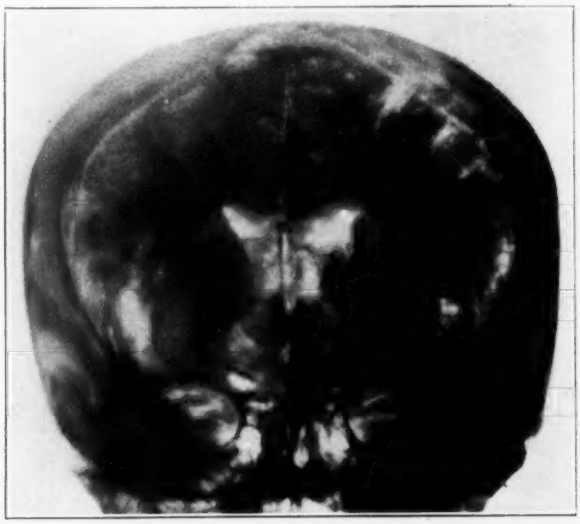

Fig. 4.—Mr. K. Encephalogram in a case of typical trigeminal neuralgia on the left, showing atrophy of the left hemisphere and collection of air over and between the atrophic gyri, enlargement of the left lateral ventricle and a lesser degree of atrophy of the right island.

ourselves of another method, which may not be conclusive but which has the advantage of being applicable to living subjects. In view of the degree of cortical and subcortical atrophy which we encountered at autopsy in cases of trigeminal neuralgia, it is not strange to discover that the same wasting of nerve tissue, and sometimes the elongation or enlargement of the lateral ventricle, can be visualized in the encephalogram (fig. 4). When the atrophy is sufficiently marked to be demonstrable with injection of air, the encephalogram, in our opinion, may be of assistance in the differentiation of typical and atypical neuralgia. Anatomic experience, as well as our physiologic considerations, therefore, favor the assumption that major trigeminal neuralgia is a special form of the thalamic syndrome.

Two questions may be raised in relation to this theory. It is indisputable that section or mere blocking of the peripheral portion of the fifth nerve relieves completely the pain of trigeminal neuralgia. What proof can be produced in support of the statement that the thalamic lesion is really the cause of the pain and not an accidental observation in a number of elderly, and presumably arteriosclerotic, persons? Second, how can it be explained that in trigeminal neuralgia pain and sensory disturbance are confined to the face?

We have been so fortunate as to find the answer to the first question in a successful therapeutic experiment.[5] A patient with all classic signs and symptoms of a thalamic hemorrhage and intolerable pain over one whole side of the body, including the face, consulted Dr. C. H. Frazier and insisted on any operation which might offer the slightest hope of improving her condition. If our theory was correct, blocking the fifth nerve should relieve the pain in the face. This proved to be the case. Thus did we conceive that cutting down the influx of afferent impulses to the trigeminal system abolishes the appearance of paroxysms.

Interesting as the result of blocking the fifth nerve was to us, it did not solve the patient's problem. Therefore, we applied our newly gained knowledge in checking by chordotomy the pain impulses from the afflicted side of the body. The patient, who had been brought to the hospital on a stretcher complaining of intolerable pain, despite administration of 9 grains (0.58 Gm.) of morphine sulfate daily, left the hospital thirteen days after operation free from pain, without the use of sedatives, and on her own feet.

The results of experiments on animals which Gammon and one of us (F. H. L.)[6] performed in Bronk's laboratory pointed in the same

5. Frazier, C. H.; Lewy, F. H., and Rowe, S. N.: The Origin and Mechanism of Paroxysmal Neuralgic Pain and the Surgical Treatment of Central Pain, Brain **60**:44, 1937.

6. Lewy, F. H., and Gammon, G. D.: The Modification of Spontaneous Cortical Activity by Sensory Stimuli, Am. J. Physiol. **123**:127, 1938.

direction. It could be demonstrated that the spontaneous electrical activity of the thalamus and cortex depended to a certain degree on, and was modified by, the continual influx of sensory impulses from all parts of the body, especially, at least in cats, from the trigeminal area.

Our second question can be answered from a review of the anatomic and clinical literature. It is established that the secondary trigeminal fibers end within the optic thalamus in the semilunar nucleus and the *centre médian* and that the face as a rule does not become involved in the case of a thalamic lesion unless the lesion is unusually extensive.[7] Finally, it is not true that pain and sensory disturbance in trigeminal neuralgia are always confined to the face. Careful inquiry and examination of the patients reveal that constant or neuralgic pain involving the brachial, intercostal or sciatic nerves and sensory anomalies, as already mentioned, are not rare attendants of trigeminal neuralgia.

With the attention fixed on the aching face, the physical signs present in patients with trigeminal neuralgia have been unduly neglected. Our statistics show that the average age of our 50 patients was 58.6 years. The majority of the values for blood pressure were approximately 185 systolic and 90 diastolic. However, not more than 6 of the 50 patients were entirely free from symptoms of vascular disease. Fifty per cent showed enlargement of the heart or murmurs, angina pectoris or signs of myocardial degeneration. In other words, over 60 per cent had definite arteriosclerosis, and almost as many had signs of renal dysfunction. It is true that this experience had more bearing on the old age group, although genuine arterial hypertension was found in some of the patients between 30 and 40 years of age. In the younger patients, indications of vasolability, such as dizziness and fainting spells, black spots before the eyes and peripheral angiospasms, were more frequent than fully developed premature angiopathy. Fourteen per cent of our patients experienced trigeminal neuralgia in two periods of life, separated by pain-free intervals of from ten to thirty-three years. They had complained of physical inconveniences referable to vasomotor instability in youth and showed high blood pressure when they came for operation in the second period of the disease. In some patients, admitted to the hospital repeatedly for injections of alcohol, the gradual and constant increase in blood pressure could be checked over a long period of years.

The early onset of vascular disease in several of the patients with trigeminal neuralgia suggested a hereditary component. In 10 per cent of our patients one or both parents died of Bright's disease. Heredofamilial occurrence of trigeminal neuralgia was observed in 6 per cent.

7. Winkler, C.; De Bouw van het Zenuwstelsel, Haarlem, E. F. Bohn, 1917, vol. 1, p. 332.

Familial and personal migraine was found in more than 20 per cent of patients suffering from trigeminal neuralgia,[8] and was combined with Parkinson's disease in 14 per cent. A clinical history may exemplify the various instances to which we have referred.

The mother of Mrs. S. suffered from trigeminal neuralgia; the brother died of chronic renal disease, and the sister experienced a paralytic stroke. The patient herself suffered from terrific headache during her first period and each of her five confinements. After rapidly successive childbirths, she had the first series of mild facial paroxysms at the age of 45. The second series, with very severe attacks, began at the age of 63. At that time the patient showed retinal angiosclerosis and a blood pressure of 185 systolic and 65 diastolic. After successful section of the fifth nerve root she was confused, disoriented, aphasic and apraxic for two weeks.

The constitutional factor in trigeminal neuralgia finds its expression not only in dynamic but in static features. In cooperation with Dr. S. M. Dupertuis, of Dr. George Draper's constitutional clinic, Columbia University, we made a complete anthropologic survey of 40 of our patients, the numerical results of which will be given elsewhere. Suffice it to state here that these patients are part of a uniform group, different in many respects from any other hitherto observed. They are representatives of the short, thick type of Hippocrates. They are heavily built and are square and chunky. The interpupillary distance is extraordinarily wide. The sitting height and the length of the thorax and arms are unproportioned to the short legs. The women show a masculine expression of the face, and the men have a pelvis of feminine diameter. The habitus of patients with typical trigeminal neuralgia is different from, even the reverse of, that of persons suffering from so-called facial neuralgia.

In their mental makeup, persons with typical trigeminal neuralgia are extrovertive, sociable, talkative, busy and good humored. Despite the excruciating pain of the attacks, they seem to have forgotten all about it once the paroxysm is over. Most characteristic is the attitude of the patients toward postoperative paresthesias. It is a mistake to believe that these puzzling sensations are less frequent with typical than with atypical neuralgia; persons with typical neuralgia, however, flatly disregard them. They do not mind them, while the patients in the atypical group mind them all the time. They ponder over them in the manner of introverts and make life unhappy for themselves, their families and their physicians.

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8. Patrick, H. T.: The Symptomatology of Trifacial Neuralgia, J. A. M. A. **62**:1519 (May 16) 1914. Paskind, H. A.: Relationship of Migraine, Epilepsy and Some Other Neuropsychiatric Disorders, Arch. Neurol. & Psychiat. **32**:45 (July) 1934.

The last interesting point in differentiation of the two groups is their behavior under the influence of drugs. Most authors agree that patients with typical tic, despite the severe pain, seldom become addicts, while those with the atypical form are in real danger of becoming addicts. Members of the first group experience no enjoyment from opiates; those of the second do. Conversely, cobra venom eases the pain of typical tic in some instances, but does not relieve the inconveniences of atypical neuralgia. This effect becomes understandable when one realizes that cobra venom acts by improving the circulation, which is diseased in patients of the typical group.

In short, trigeminal neuralgia is a special form of the thalamic syndrome, caused by functional or organic vascular insufficiency. Sufferers from major trigeminal neuralgia seem likely to belong in a group of persons of uniform hereditary and constitutional physical habitus and mental makeup, with a tendency to cardiorenal angiopathies. This fact may explain why experienced neurologists and neurosurgeons, in judging a patient with trigeminal neuralgia, have an intuitive, yet distinct, feeling for the type of person who probably will or will not be benefited by section of the fifth nerve.

SUMMARY

1. Quantitative disturbances of sensibility play a contributory rather than an essential role in trigeminal neuralgia. Qualitative disturbances are preeminent in frequency and significance.

2. This change in the pattern of the sensory impulses together with the motor signs and symptoms points to the optic thalamus as the probable site of a lesion in trigeminal neuralgia.

3. In 6 cases of major trigeminal neuralgia the brain showed atrophy of the ipsilateral hemisphere, with widening of the lateral ventricle which could be visualized in an encephalogram during life. The foci of softening were located either within the lateral and medial nuclei of the optic thalamus or in the thalamocortical tract. In the latter case the ipsilateral semilunar nucleus and the *centre médian* of the thalamus were atrophied.

4. The lesions were observed to be angiopathies. Clinical examination of 50 persons with trigeminal neuralgia showed signs of arteriosclerosis and renal dysfunction in 30.

5. The frequent occurrence of heredofamilial stigmas in cases of trigeminal neuralgia led to an anthropologic examination of 40 patients, showing that these persons belong in a uniform group, differing in physical habitus and mental makeup from persons suffering from atypical facial neuralgia.

STUDIES IN DISEASES OF MUSCLE

VII. EFFECT OF KETOSIS AND OF THE INGESTION OF CREATINE IN MYOTONIA CONGENITA

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In a previous report of this series [1] it was shown, in agreement with Findlay [2] and Rosenbloom and Cohoe,[3] that in adults with myotonia congenita the urinary output of creatinine and creatine is normal. It was shown further that the creatine tolerance [4] and the effects of aminoacetic acid on the metabolism of creatine in persons with this condition are similar to those observed in normal persons. Moreover, functional disturbances of the muscles, such as adventitious movements and increased resistance to passive stretch, were observed by us [1] to be without effect on the metabolism of creatine. Considered together, these findings suggest that there is no essential relationship between the functional defect (myotonia) in myotonia congenita and the metabolism of creatine.

However, Poncher and Woodward,[5] on the basis of their studies, recently postulated such a relationship. They observed an increase in the myotonia of 2 patients with myotonia congenita when creatine was administered. In 1 patient, a boy aged 5 months, the creatinuria normally present in infancy was absent. When thyroid substance was administered, creatinuria followed and was accompanied by improved muscular function and loss of myotonia. However, when creatine was ingested the symptoms returned. Administration of thyroid substance to the second patient, a man aged 22 years, induced neither creatinuria

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1. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: V. Metabolism of Creatine and Creatinine in Myotonia Congenita, Myotonia Atrophica, Amyotonia Congenita, Dystonia Musculorum Deformans and Paralysis Agitans, Arch. Neurol. & Psychiat. **40**:680 (Oct.) 1938.

2. Findlay, L.: A Case of Thomsen's Disease, Quart. J. Med. **5**:495, 1912.

3. Rosenbloom, J., and Cohoe, B. A.: Chemical and Metabolism Studies in a Case of Myotonia Congenita—Thomsen's Disease, Arch. Int. Med. **14**:263 (Aug.) 1914.

4. Creatine tolerance in the percentage retention of ingested creatine.

5. Poncher, H. G., and Woodward, H.: Pathogenesis and Treatment of Myotonia Congenita, Am. J. Dis. Child. **52**:1065 (Nov.) 1936.

nor improvement in the symptoms, but the ingestion of creatine was followed by an exacerbation of the muscular defect.

We [1] observed no change in the metabolism of creatine in a patient with myotonia atrophica when thyroid substance was given. Furthermore, the muscular defect (myotonia) was not improved under these conditions; in fact, the difficulty in relaxing the muscles may have been increased during the period in which thyroid substance was administered. Ingestion of 1.32 Gm. of creatine by this patient with myotonia atrophica was without effect on the symptoms.

The present investigations were made in order to study further whether the metabolism of creatine is related in any way to the muscular defect in myotonia congenita. Two methods of study were used. The first was that of administering large amounts of creatine to a patient with this condition. The second method was induction of ketosis in a patient with myotonia congenita by the use of a diet containing large amounts of fat and only small amounts of carbohydrate (ketogenic diet).

It has been maintained by some investigators (Cathcart,[6] and McCollum and Hoagland [7]) that fasting or deprivation of carbohydrates will induce creatinuria. On the other hand, Loebel [8] observed that restriction of carbohydrates sufficient to induce ketosis, even for long periods, was without effect on the urinary output of creatine. However, from the data reported by the many workers who have investigated the problem it appears that in certain instances of advanced carbohydrate deprivation (Cathcart [6b]) or of acidosis due to a variety of causes (Riesser and Brentano [9]) creatinuria may occur. It was for this reason that the induction of ketonuria by means of diets low in carbohydrates was used in an attempt to influence the metabolism of creatine and to study the effect of such a change on the muscular defect in myotonia congenita.

HISTORY IN A CASE

A man aged 30 complained of muscular rigidity of lifelong duration. Since early childhood he had been unable to relax the grasp quickly after initially taking hold of an object. After a few contractions this defect disappeared, only to reappear

6. Cathcart, E. P.: (*a*) The Influence of Carbohydrates and Fats on Protein Metabolism, J. Physiol. **39**:311, 1909; (*b*) Influence of Fat and Carbohydrate on the Nitrogen Distribution of the Urine, Biochem. J. **16**:747, 1922.

7. McCollum, E. V., and Hoagland, D. R.: Studies of the Endogenous Metabolism of the Pig as Modified by Various Factors: II. The Influence of Fat Feeding on Endogenous Nitrogen Metabolism, J. Biol. Chem. **16**:317, 1913.

8. Loebel, R. O.: The Relation of Fat Oxidation to Phosphocreatine Metabolism and Creatinuria, J. Clin. Investigation **13**:713, 1934.

9. Riesser, O., and Brentano, C.: Untersuchungen über die Entstehung der Kreatinurie: I. Azidose und Kreatinuria, Arch. f. exper. Path. u. Pharmakol. **155**:1, 1930.

after a period of rest. When he attempted to walk after having rested for at least several minutes, the muscles of the legs became stiff during the first few steps, and he often had difficulty in keeping his balance. The muscular stiffness was most pronounced just after he had awakened in the morning. He stated that after taking alcoholic beverages the defect was less evident. Exposure to low temperatures, emotional stress and periods of muscular inactivity increased the difficulty in relaxing the muscles. A brother, a sister and 2 of his children had a similar disability. The past personal history was not important.

Examination revealed the defect described. The muscles were well developed and prominent.

Effect of Ketosis and of Ingestion of Creatine on the Metabolism of Creatine and Creatinine in Myotonia Congenita

Daily Diet (Creatine Free)	Total Urinary Nitrogen Daily, Gm.	Urinary Creatinine* Daily, Gm.	Urinary Creatine† Daily, Gm.	Urinary Acetone Daily, Gm.	Creatine‡ Given per Os, Gm.	Creatine‡ Retained Gm.	Creatine‡ Retained %
General.....	8.25	2.060	0				
	8.30	1.941	0.013				
	8.47	1.980	0.008				
	9.26	1.883	0.012				
	10.40	1.860	2.050		10	7.29	72.9
	7.20	1.451	0				
	9.12	1.875	0				
	9.58	1.730	2.690		15	11.40	76.0
	8.08	1.685	1.695		10	7.76	77.6
	7.80	2.090	0.030				
	10.00	2.090	0				
Protein..... 60 Gm.	11.15	2.030	2.640		15	11.51	76.7
Fat..... 90 Gm.							
Carbohydrate 250 Gm.	12.71	2.000	3.360		15	10.56	70.4
	9.84	2.065	0.013				
	10.15	1.940	0.013				
Protein..... 50 Gm.	10.30	1.955	0.021	Trace			
Fat..... 200 Gm.							
Carbohydrate 25 Gm.	11.27	1.842	0.011	0.298			
	11.75	2.000	2.820	0.595	10	6.28	62.8
	9.98	1.940	0	1.362			
	11.73	2.065	0.025	1.780			
	9.46	1.851	0.102	2.230	1.32	1.22	92.7
	8.85	1.908	0.033	1.480			
	8.46	1.885	0.032	2.110			

* Preformed creatinine.
† Urinary creatine is expressed as creatinine.
‡ Expressed as crystalline creatine. Creatine as purchased (air-dried crystals) contains 1 molecule of water. Therefore, 1.32 Gm. of creatine (with 1 molecule of water) = 1.16 Gm. of creatine (water free) = 1 Gm. of creatinine. 10 Gm. of creatine (with 1 molecule of water) = 8.79 Gm. of creatine (water free) = 7.58 Gm. of creatinine. 15 Gm. of creatine (with 1 molecule of water) = 13.19 Gm. of creatine (water free) = 11.38 Gm. of creatinine.

METHODS

The methods used were similar to those described in the first report of this series.[10] During the periods of investigation the patient was in a special metabolism ward, where accurate collections of urine could be made, and the diet was rigorously supervised. The observations were divided into three periods: In the first the patient was given a general diet unrestricted in the amounts of protein, fat and carbohydrate, but free from creatine and creatinine; in the second the diet con-

10. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: I. Metabolism of Creatine and Creatinine in Progressive Muscular Dystrophy, Arch. Neurol. & Psychiat. **38**:992 (Nov.) 1937.

tained 60 Gm. of protein, 90 Gm. of fat and 250 Gm. of carbohydrate daily, and in the third period, 50 Gm. of protein, 200 Gm. of fat and only 25 Gm. of carbohydrate. All the diets were free from creatine and creatinine. The urine was collected carefully in twenty-four hour specimens, and the amounts of creatinine, creatine and nitrogen were determined daily, according to the methods previously described.[10] When the urine contained ketone bodies, these were determined daily by the technic of Van Slyke [11] and were removed from the urine by the method of Blau [12] prior to the estimation of the creatinine and creatine.

OBSERVATIONS

The data on the metabolism of creatine are given in the accompanying table. There was no spontaneous creatinuria, and the amounts of creatinine eliminated were normal during all the periods of observation. When creatine was ingested in amounts of 10 and 15 Gm., from 63 to 78 per cent was retained. The amount of creatine retained by the patient was from 6.28 to 7.76 Gm. on the days when 10 Gm. was administered and from 10.56 to 11.51 Gm. when 15 Gm. was given. Retention of these large amounts of creatine was without demonstrable effect on the ability of the patient to relax the muscles after an initial forceful contraction (myotonia). Furthermore, deprivation of carbohydrates which resulted in ketosis, even to the extent of inducing daily urinary excretion of as much as 2.23 Gm. of ketone bodies, was without effect on the metabolism of creatine or on the patient's symptoms. Throughout the six weeks of study, close observation disclosed no effect of ketosis or of the ingestion of large amounts of creatine on the muscular defect.

COMMENT

The metabolism of creatine is commonly involved in diseases of the muscles in which muscular wasting occurs (Milhorat and Wolff [13]). However, in adult patients with myotonia congenita, unless muscular wasting should be present for any reason, the output of creatine and the creatine tolerance usually are normal.

In the observations of this study there was no evidence of any defect in the metabolism of creatine, findings which confirm those by Findlay,[2] Rosenbloom and Cohoe [3] and us.[1] Furthermore, there appeared to be no relationship between the metabolism of creatine and the muscular defect of the patient studied in these investigations. When creatine was given in such large amounts as to induce retention of as much as 11.51 Gm., there was no effect on the muscular symptoms. Poncher and Woodward [5] observed an increase in the myotonia of their adult patient when only 3 Gm. of creatine was administered daily.

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11. Van Slyke, D. D.: Studies in Acidosis: VII. The Determination of B-Hydroxybutyric Acid, Aceto-Acetic Acid, and Acetone in Urine, J. Biol. Chem. **32**:455, 1917.

12. Blau, N. F.: The Estimation of Creatinine in the Presence of Acetone and Diacetic Acid, J. Biol. Chem. **48**:105, 1921.

13. Milhorat, A. T., and Wolff, H. G.: Studies in Diseases of Muscle: IV. Metabolism of Creatine and Creatinine in Muscular Wasting Subsequent to Disease of the Nervous System, Arch. Neurol. & Psychiat. **40**:663 (Oct.) 1938.

The use of a ketogenic diet and the induction of ketosis sufficient to cause excretion of over 2 Gm. of urinary ketone bodies daily were without effect on the patient's symptoms. Furthermore, in these studies no effect of the ketosis on the metabolism of creatine was found. These findings are in agreement with those of Lobel,[8] who did not observe any creatinuria in patients with diabetes mellitus or idiopathic epilepsy who were maintained on a ketogenic diet for long periods. One of the first workers to investigate this problem was Cathcart,[6a] who observed that during starvation creatine is constantly present in the urine. When carbohydrate was given he found that the amounts of urinary creatine fell, but when fat was ingested the output of creatine was increased. On the other hand, Graham and Poulton [14] were unable to induce creatinuria by deprivation of carbohydrates and suggested that the findings of Cathcart may have been due to error in the determination of the creatine and creatinine. In his earlier work Cathcart failed to remove the ketone bodies in the urine before determining the amounts of creatine and creatinine. It is now well known that ketone bodies in the urine interfere with the colorimetric estimation of creatine and creatinine and that unless the necessary precautions are taken erroneous results will be obtained. However, in the later work of Cathcart and Orr,[15] McCollum and Hoagland [7] and Cathcart [6b] the possibility of this error was avoided. These authors found that creatinuria may develop after the use of diets containing small amounts of carbohydrate, even when ketosis had not been induced.

Riesser and Brentano [9] observed that acidosis due to a variety of causes is accompanied by creatinuria, and Brentano [16] related the creatinuria to diminution in the amounts of glycogen in the muscles. When there was no diminution in the amounts of glycogen in the muscles no creatinuria occurred. Other measures which also caused lowering in the amounts of glycogen in the muscles were observed by Brentano to induce creatinuria. Unfortunately, Brentano failed to remove the ketone bodies that may have been present in the urine before making the determinations of creatine and creatinine, so that some of his observations on creatinuria in ketosis are open to question.

It is possible, judging from the work of Brentano,[16] that ketosis of greater magnitude or of longer duration than was used in these studies

14. Graham, G., and Poulton, E. P.: The Alleged Excretion of Creatine in Carbohydrate Starvation, Proc. Roy. Soc., London, s.B **87**:205, 1914.

15. Cathcart, E. P., and Orr, J. B.: The Influence of Carbohydrate and Fat on Protein Metabolism: III. The Effect of Sodium Selenite, J. Physiol. **48**:113, 1914.

16. Brentano, C.: Untersuchungen über die Entstehung der Kreatinurie: II. Die Beziehungen zwischen Kreatinurie und Muskelglykogen, Arch. f. exper. Path. u. Pharmakol. **155**:21, 1930.

might induce spontaneous creatinuria or lower the creatine tolerance. However, when the proper precautions were taken in removing the ketone bodies from the urine before making the determinations of creatine and creatinine, definite ketosis for seven days was found to have no effect on the metabolism of creatine.

The absence of any effect on the output of creatinine when creatine was administered under the conditions of these experiments is in agreement with the findings of previous workers. Thus, Chanutin [17] observed no significant increase in the excretion of creatinine for four days when 10 Gm. of creatine was ingested daily. However, the continued ingestion of this amount of creatine was followed by a definite increase in the output of creatinine.

The site of the defect in myotonia congenita is still unknown, although it appears from recent studies, notably those of Kennedy and Wolf,[18] that peripheral structures are primarily involved. Nevertheless, the results of the present investigation demonstrate that the metabolism of creatine is not related significantly to the muscular defect in myotonia congenita.

SUMMARY AND CONCLUSIONS

The metabolism of creatine and creatinine in a patient with myotonia congenita given a ketogenic diet was studied. During two periods of observation when the diet contained adequate amounts of carbohydrate and one period when the diet contained such small amounts of carbohydrate that pronounced ketonuria was induced the output of creatine and creatinine was normal, and the creatine tolerance was not unusual. Ketosis was without effect on the metabolism of creatine or on the patient's symptoms.

Administration of large amounts of creatine sufficient to induce the retention of over 11 Gm. by the patient in no way influenced the muscular defect.

The results offer no evidence of any essential relationship between the metabolism of creatine and the muscular symptoms in myotonia congenita.

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17. Chanutin, A.: The Fate of Creatine When Administered to Man, J. Biol. Chem. **67**:29, 1926.

18. Kennedy, F., and Wolf, A.: Quinine in Myotonia; Prostigmine in Myasthenia: A Clinical Evaluation, J. A. M. A. **110**:198 (Jan. 15) 1938.

EVALUATION OF ARTIFICIAL FEVER THERAPY FOR NEUROPSYCHIATRIC DISORDERS

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OMAHA

Modern interest in fever therapy began with the monumental contribution of Wagner von Jauregg [1] in 1917, proving the curative value of malarial therapy in cases of dementia paralytica. For the first fifteen years extensive experimentation was carried on by means of biologic, chemical and infectious induction of body fever by so-called nonspecific foreign protein shock. More recently extensive investigations with various physical methods of artificial fever production have been carried out. After twenty-five years of clinical application of various methods, one can state that artificial fever therapy has a permanent place in medical therapeutics. However, the significance of body fever and its relation to the course of disease is as yet not fully understood.

After ten years of experience with malarial fever in treatment of paralytic dementia, in spite of the excellent results often reported, my personal results have been far from satisfactory. The inherent dangers of engrafting one serious disease on another, with the inescapable mortality and morbidity of malarial fever, lead me to believe that the use of this method is empiric and that it is not a permanently sound therapeutic procedure. A careful, open-minded study of other forms of fever therapy convinced me that malarial inoculation will gradually be replaced by safer, more readily controlled and efficient forms of artificial fever therapy. The production of frequent remissions in dementia paralytica by other biologic and chemical agents, such as typhoid vaccine and sulfur in oil, in malaria-resistant patients further convinced me that malarial inoculation is a nonspecific method. Malarial fever is essentially a foreign protein shock febrile reaction, the protein being set free at the time of segmentation of the plasmodia. The curative factor is probably the febrile reaction, not the agent that produces the fever.

Certain ardent enthusiasts for malarial therapy contend that there is something specific in malaria which acts through stimulation of the reticuloendothelial system and the increased production of clasmatocytes in the peripheral blood. It has been suggested that in the treatment of

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From the Departments of Neuropsychiatry and Fever Therapy Research, the University of Nebraska College of Medicine. Membership thesis, American Neurological Association, 1937.

1. Wagner von Jauregg, J.: Ueber die Einwirkung der Malaria auf die progressive Paralyse, Psychiat.-neurol. Wchnschr. **20**:132 (Aug. 31) 1918.

syphilis these phagocytic cells provide an important cellular weapon of defense which is not available when other fever methods are employed.

Doan,[2] however, has recently shown a large increase in phagocytic cells in other tissues, especially the lymph nodes, spleen and liver, from physical induction of artificial fever. He expressed the belief not only that the thermal factor, important in the inactivation of Spirochaeta pallida, is present in the physical induction of heat but that there is exerted a profound effect on the cellular equilibrium of the body in the directions most effective in mobilization of the defense forces of the body.

Bessemans and his co-workers,[3] ten years ago, found that spirochetes in primary and secondary local lesions can be destroyed by a variety of agencies producing fever that the human body can tolerate. Boak, Carpenter and Warren,[4] Simpson [5] and others confirmed these observations that S. pallida is thermolabile, that sustained temperatures of 105 or 106 F. markedly inhibit or destroy the organism. When the spirochetes have invaded deeper body tissues they tend to become more heat resistant; thus, combined fever and chemotherapy are more effectual in destroying the parasites than either agent alone.

In addition to these experimental studies, malarial therapy has been challenged of late years by the clinical application of physically induced artificial fever, and increasing numbers of cases of resistant neurosyphilis are being reported in which there were favorable results. Many methods, such as the use of prolonged hot baths, hot air, radiothermy, diathermy, infra-red and carbon filament light cabinets and the electric blanket, have been successful. Accumulation of clinical and experimental evidence seems to indicate that the common denominator of all

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2. Doan, C. A.: Differential Reaction of Bone Marrow, Connective Tissue, and Lymph Nodes to Hyperpyrexia, Tr. Internat. Conf. Fever Therapy **1**:41, 1937.

3. Bessemans, A.; de Potter, F., and Hacquaert, R.: Sur deux formes d'aéro-thermothérapie locale des syphilones testiculaires primaires du lapin, Compt. rend. Soc. de biol. **100**:757 (March 15) 1929. Bessemans, A.; Vercoullie, J., and Hacquaert, R.: Influence de diverses applications locales de la chaleur sur les accidents syphilitiques primaires et secondaires chez l'homme, ibid. **101**:483 (June 14) 1929. Bessemans, A.: The Local Application of Heat as an Adjunct in the Social and Individual Prophylaxis of Syphilis, Urol. & Cutan. Rev. **34**:71 (Feb.) 1930. Bessemans, A.; van Haelst, J., and de Wilde, H.: An Experimental Study of the Problem of the Existence of an Invisible Form of the Syphilitic Virus, and of Spontaneous Spirochetosis in Rabbits, Am. J. Syph. & Neurol. **19**:161 (April) 1935. Bessemans, A.: Nouvelles données expérimentales sur hyperthermie médicale, Rev. belge sc. méd. **9**:569 (Nov.) 1937.

4. Boak, R.; Carpenter, C. M., and Warren, S. L.: Studies on Physiological Effects of Fever Temperatures: The Thermal Death Time of Treponema Pallidum in Vitro with Special Reference to Fever Temperatures, J. Exper. Med. **56**: 741 (Nov.) 1932.

5. Simpson, W. M.: Artificial Fever Therapy of Syphilis, J. A. M. A. **105**: 2132 (Dec. 28) 1935.

methods, whether employing infectious, biologic, chemical or physical means, is simply increased body temperature or artificial fever.

The physiologic reactions produced by elevated body temperature in speeding up biophysical and chemical processes, such as oxidation in resistance to infections, are only partially understood. Fever per se increases the velocity of the blood, produces vasodilation and elevates the basal metabolism (7 per cent for each degree of rise in temperature), increases leukocytosis and phagocytosis and inhibits or destroys certain bacteria. Other profound changes in metabolism, blood chemistry and mobilization of immune bodies occur in the defense against infection as a result of fever, but exact knowledge of the mechanism is still lacking. I have reviewed elsewhere [6] the present status of knowledge of fever therapy.

After experimentation with various physical methods, I became most interested in the air-conditioned cabinet (Kettering-Simpson hypertherm) because of its relative safety and simplicity. In 1934, through cooperation of the Kettering Institute for Medical Research, the Miami Valley Hospital, Dayton, Ohio, and the dean of the University of Nebraska College of Medicine, I was permitted to organize a department of fever therapy research. During this three year period, my colleagues and I have carried out extensive fundamental and clinical investigations on a large number of diseases, in an attempt to evaluate the proper place of artificial fever therapy. A total of 766 patients have been given 3,539 artificial fever treatments. Of these, 244, or 32 per cent, had neuropsychiatric disorders. They received 1,591 treatments, or 45 per cent of the total number given. The results of our investigations on the neuropsychiatric disorders form the basis of this paper.

RESULTS OBTAINED IN CASES OF NEUROSYPHILIS BY COMBINED ARTIFICIAL FEVER THERAPY AND CHEMOTHERAPY

In the department of fever therapy research of the University of Nebraska, 90 patients with various stages of neurosyphilis have completed treatment in the past three years. They received 809 fever treatments. Sufficient lapse of time (from three to thirty months) and adequate follow-up data have provided opportunity for an evaluation of results in 66 cases, which have been classified as follows:

	Number of Cases
1. Asymptomatic neurosyphilis	8
2. Meningovascular neurosyphilis	12
3. Dementia paralytica (both cerebral and tabetic)	21
4. Tabes dorsalis	25
Total	66

6. Bennett, A. E.: Artificial Fever Therapy, in Blumer, G.: The Practitioners' Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1937, vol. 3 (supp. index), pp. 242-248.

ASYMPTOMATIC NEUROSYPHILIS

It is our belief that studies of the spinal fluid made as a routine within the first year of syphilitic infection enable one to make a diagnosis of asymptomatic neurosyphilis. In a personal study [7] of 57 patients during the first year of the disease I found abnormal changes in the cerebrospinal fluid in 31 per cent.

It is our further belief that grave clinical neurosyphilis develops in this group. Thus, an early diagnosis with adequate therapy should prevent later grave manifestations. However, in spite of active vigorous chemotherapy, early asymptomatic neurosyphilis progresses to active clinical neurosyphilis in about 3 to 8 per cent [8] of cases. In these cases some form of fever therapy should be given. Accumulated clinical evidence indicates that fever therapy adequately prevents clinical neurosyphilis.

Influence of Fever Therapy in Prevention of Late Neurosyphilis.—An interesting observation is that of Needles.[9] As a result of extensive experience in the tropics with thousands of patients with syphilis in a region where malaria is endemic, he found that 31 per cent were syphilitic. Of about 12,000 patients, however, he found only 1 with neurosyphilis, and that patient had never had malaria. He concluded that endemic malaria probably prevents neurosyphilis.

O'Leary,[10] in a study of 89 patients with the resistant type of asymptomatic neurosyphilis, added malarial inoculation to his treatment. These patients had an average of twelve malarial febrile paroxysms, with no other follow-up treatment. After six months he found the serologic reactions of the spinal fluid partially or completely reversed in 77 per cent of the patients. He concluded that malarial therapy is indicated in all cases of resistant asymptomatic neurosyphilis in which a serologic reversal fails to occur after routine chemotherapy, there is a tendency to progression of the cerebrospinal fluid formula to the type characteristic of dementia paralytica or subjective or objective symptoms of clinical neurosyphilis develop.

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7. Bennett, A. E.: Studies in Early Asymptomatic Neurosyphilis, Nebraska M. J. **14**:400 (Oct.) 1929.

8. O'Leary, P. A., and others: Cooperative Clinical Studies in Treatment of Syphilis: Asymptomatic Neurosyphilis, Ven. Dis. Inform. **18**:17 (March) 1937.

9. Needles, R. J.: Effect of Endemic Malaria on the Incidence of Neurosyphilis, Arch. Neurol. & Psychiat. **34**:618 (Sept.) 1937.

10. O'Leary, P. A.: Malaria Therapy in the Treatment of Neurosyphilis, Ann. Int. Med. **7**:1513 (June) 1934.

It is also worthy of note that patients who received adequate routine chemotherapy and later malarial fever treatment showed no clinical progression of neurosyphilis, whereas those who received an inadequate amount of arsphenamine and heavy metals prior to malarial therapy showed progression to the serious stages of dementia paralytica, tabes dorsalis, meningovascular syphilis or optic atrophy.

As already stated, in recent years the weight of cumulative clinical and experimental evidence indicates that in malarial therapy fever alone is the agent which prevents and cures the late sequelae of neurosyphilis. After three years of clinical trial of artificial fever treatment combined with chemotherapy, we believe that both the prevention and the cure of neurosyphilis were more effective than after therapeutic measures previously described.

Results Obtained in Treatment of Asymptomatic Neurosyphilis.—Our results may be summarized as follows:

In this group were 8 patients, all men, with ages varying from 32 to 58. The duration of the infection ranged from twelve to thirty years. All the patients had had many years of intensive routine chemotherapy; all were considered to be "Wassermann fast," and all had strnogly positive reactions of the cerebrospinal fluid.

The treatment was artificial fever therapy for from twenty-nine to fifty hours, in 10 sessions of three or five hours at a temperature of from 105 to 106 F., combined with 0.06 Gm. of mapharsen (metaaminoparahydroxyphenylarsine oxide hydrochloride) at weekly intervals.

The results obtained in this group were as follows: The serologic reactions of the cerebrospinal fluid were completely reversed in 5 patients, partially reversed in 2 and unchanged in 1. (The last patient had only twenty-nine hours of fever therapy.)

Combined artificial fever therapy and chemotherapy constitutes the indicated method of treating resistant asymptomatic neurosyphilis. Almost uniformly satisfactory serologic response can be expected, and progression to active neurosyphilis can usually be prevented.

MENINGOVASCULAR NEUROSYPHILIS

Twelve patients completed the prescribed course of treatment with sufficient follow-up data to report. There were 6 men and 6 women; the ages varied from 23 to 59. The majority of the men patients were seriously ill with complicating vascular disorders, such as aortitis or hypertension; 8 patients had had previous intensive routine chemotherapy and 4 had had no previous therapy.

The entire group presented almost completely disabling neurologic symptoms and findings: Four had hemiparetic features; 3, palsies of the cranial nerves; 1, a syndrome resembling multiple sclerosis; 3, chronic headaches, indicating intracranial pressure and meningitic phenomena, and 3, aphasic, convulsive and confusional psychotic reactions.

The treatment given was from twenty-five to fifty hours of artificial fever in from three to five sessions, at a temperature of from 105 to 106 F., combined with mapharsen and bismarsen.

The clinical results were complete relief from all symptoms, except in the case of 1 patient with hemiplegia and 1 with occasional convulsions. Striking improvement was seen in the aphasic and meningitic symptoms. At least half the patients would have been unable to withstand malarial therapy. Because of myocardial and vascular complications, many of the patients presented difficulties in carrying them successfullly through fever therapy. The great advantage in controlling the height and duration of induced fever was particularly apparent in this group of patients.

The serologic results in this group were as follows: The reactions of the cerebrospinal fluid were completely reversed to negative in 4 patients, markedly improved to date in 3, unchanged in 1 and negative throughout in 1. For 3 patients the present serologic reactions have not been obtained.

DEMENTIA PARALYTICA

At the University of Colorado Psychopathic Hospital, Barnacle, Ebaugh and Ewalt [11] have conducted a comparative study of malarial therapy followed by tryparsamide and the method of fever induction with the Kettering hypertherm combined with administration of tryparsamide. This study is the only one of its kind of which I am aware. A recent personal report from these investigators gave the following results for the period from February 1935 to September 1937.

Treatment of 100 patients with dementia paralytica has been completed; 50 received treatment with tryparsamide and artificial fever induced with the hypertherm, and 50, therapeutic malaria followed by tryparsamide. The clinical and serologic results may be tabulated as follows:

	Hypertherm and Tryparsamide		Therapeutic Malaria Followed by Tryparsamide	
Clinical Results	No. of Patients	Percentage	No. of Patients	Percentage
Complete arrest	23	46	11	22
Incomplete arrest	14	28	19	38
No improvement	7	14	13	26
Death during treatment	2	4	2	4
Death after treatment	4	8	5	10
Total	50	100	50	100

	Hypertherm and Tryparsamide		Therapeutic Malaria Followed by Tryparsamide	
Serologic Results	No. of Patients	Percentage	No. of Patients	Percentage
Negative	14	28	4	8
Greatly improved	8	16	11	22
Moderately improved	8	16	8	16
Unchanged	5	10	12	24
Not checked or patient dead	15	30	15	30
Total	50	100	50	100

11. Barnacle, C. H.; Ebaugh, F. G., and Ewalt, J. R.: Treatment of Dementia Paralytica: Comparative Study of Combined Artificial Hyperpyrexia and Tryparsamide Versus Therapeutic Malaria, J. A. M. A. **107**:1031 (Sept. 26) 1936.

These results indicate approximately 20 per cent better clinical and serologic results from combined chemotherapy and artificial fever therapy than from therapeutic malaria followed by chemotherapy.

Results in Our Clinic.—For 21 patients with dementia paralytica (including 4 with the tabetic type) there were adequate follow-up data.

Of 18 men and 3 women, of ages varying from 29 to 58, 3 had had no previous treatment; 13, previous intensive chemotherapy; 1, chemotherapy together with Swift-Ellis injections; 2, malarial therapy without definite improvement; 1, Swift-Ellis and malarial therapy, and 1, typhoid vaccine fever therapy.

The entire group presented psychotic symptoms characteristic of dementia paralytica, with marked sensorial changes. About half were of the simple demented type, and half, of the expansive type. All patients were incapacitated for useful work. About half the patients required hospitalization, and one-half were outpatients during the course of treatments. All had strongly positive reactions of the spinal fluid.

The treatment given was from twenty-three to ninety-four hours of artificial fever, at a temperature of from 105 to 106 F., in from 6 to 18 sessions of from three to five hours each at weekly intervals, combined with either mapharsen or bismarsen (bismuth arsphenamine sulfonate).

The clinical results were as follows: Thirteen patients had complete arrest of the disease with full remission and return to the former occupational status; 6, moderate improvement and social recovery, but with residual symptoms; 2, persistent convulsive phenomena, and 2, no improvement.

The serologic results were: The cerebrospinal fluid reactions were completely reversed to negative in 8 patients, partially reversed in 6, unchanged in 6 and unknown in 1.

By means of another experiment, we are attempting to evaluate various forms of therapy for neurosyphilis. Treatments are being given in the Nebraska State Hospitals for mental disease to all patients with dementia paralytica who have had malarial therapy or tryparsamide without obtaining a complete remission. These patients will be given combined fever therapy and mapharsen. It is probable that by means of such clinical experiments we shall be able within a few years to evaluate properly the results of various methods of fever therapy and to determine which method will give the highest percentage of remissions.

TABES DORSALIS

A preliminary report of the results obtained in 14 patients has been made.[12] Since, there are adequate follow-up data on 25 patients in this series.

There were 16 men and 9 women, of ages varying from 27 to 69. Only 3 patients had had no previous treatment; 13 had had intensive chemotherapy, and 6, special therapy, such as malarial fever and Swift-Ellis injections in addition; in the case of 3 patients ths previous treatment was not known.

The majority of this group of patients presented severe types of tabes, with resistant symptoms and previous therapeutic failures. Almost half the group

12. Bennett, A. E.: Fever Therapy in Tabes Dorsalis, J. A. M. A. **107:** 845 (Sept. 12) 1936.

were of the so-called burned-out, seronegative type, which is notoriously unresponsive to therapy. The predominant symptoms were: root pains and gastric crises, in 17 patients; ataxia, in 7 patients, and "cord bladder," in 2 patients.

The treatment given in this group was artificial fever, at a temperature of from 105 to 106 F., for from nineteen to seventy hours, in from 10 to 15 sessions of from three to five hours each at weekly intervals, combined with bismarsen (bismuth arsphenamine sulfonate).

The clinical results included complete relief from symptoms in 18 patients (largely those with lightning pains and gastric crises); from moderate to slight relief in 5 and no improvement in 2; 1 of the patients had recurrence of pains to about the same extent as before treatment. In another patient the disease progressed to dementia paralytica after a prolonged period of relief.

The serologic results were: complete reversal to negative in 5 patients, partial reversal in 3 and no change in 3. The reaction was negative throughout in 11 patients and was unknown in 3.

ALL TYPES OF CLINICAL NEUROSYPHILIS

Combined artificial fever and chemotherapy constitute the safest and most satisfactory method of managing severe grades of neurosyphilis. Patients with meningovascular types and chronic resistant tabetic states who present serious cardiovascular problems and would be unable to withstand malarial therapy can be markedly improved. The percentage of remissions in dementia paralytica is slightly higher after this treatment than after malarial therapy; serologic reversals follow more quickly.

MULTIPLE SCLEROSIS

Evaluation of therapy for this disease is exceedingly difficult, first, because of the tendency to spontaneous remission and, second, because of the psychic reactions of the patients. Frequently, in advanced stages of the disease patients are euphoric and report improvement which cannot be confirmed by objective study.

A previous therapeutic study of nonspecific protein shock fever therapy by the use of typhoid vaccine [13] led us to carry on extensive investigations on the effects of physical fever therapy for multiple sclerosis. I am aware of reports by others, particularly Neymann and his co-workers,[14] who described marked and sustained improvement from fever therapy.

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13. Young, G. A., and Bennett, A. E.: Non-Specific Protein (Typhoid Vaccine) Therapy in Disseminated Sclerosis, Nebraska M. J. **12**:401 (Nov.) 1927; Non-Specific Protein Therapy of Multiple Sclerosis, in Blumer, G.: Forchheimer and Billings' Therapeusis of Internal Diseases, New York, D. Appleton and Company, 1929, pp. 699-712.

14. Neymann, C. A.: Hyperpyrexia Produced by Physical Agents, in Mock, H. E.; Pemberton, R., and Coulter, J. S.: Principles and Practice of Physical Therapy, Hagerstown, Md., W. F. Prior Company, Inc., 1934, vol. 1, chap. 17. Neymann, C. A., and Osborne, S. L.: The Treatment of Some Multiple Scleroses by Electropyrexia, J. Nerv. & Ment. Dis. **79**:423 (April) 1934.

We have completed the treatment of 35 patients with multiple sclerosis with from one to three courses of 6 treatments each, with an average for each patient of 8 treatments of from three to five hours each, at a temperature of from 103 to 105 F. These patients were divided into three groups: (1) 9 patients with early stages of the disease, all of whom showed unmistakable symptoms of involvement of the cranial nerves and spastic and ataxic signs, but were ambulatory without assistance; (2) 15 patients with moderately advanced stages, who were almost completely disabled, owing to marked involvement of the cerebellar and pyramidal tracts, and usually required some form of assistance to be ambulatory, and (3) 11 patients with advanced stages, all in wheel chairs or bedridden.

Results Obtained.—1. Early Stages: Five of 9 patients (55 per cent) showed from moderate to marked improvement in palsies of the cranial nerves, ataxia and body weight. None showed a remission of definite signs of involvement of the pyramidal tracts, and the improvement reported was more subjective than objective. Several of these patients have had relapses, but are still ambulatory.

2. Moderately Advanced Stages: Five of fifteen patients (33 per cent) showed from slight to moderate improvement. A number of patients had a relapse and returned for further treatment. Again, the improvement noted was largely subjective.

3. Markedly Advanced Stages: Two of 11 patients (18 per cent) seemed to show slight improvement. Two patients were made distinctly worse. Several patients in this group reported that they had subjective improvement, which could not be confirmed by objective findings. Euphoric mental reactions are often present and appear tragic when the patient is bedridden.

As a result of extensive experience during a period of three years with a large number of patients with multiple sclerosis we have concluded that artificial fever therapy produces no permanent therapeutic effects which alter the course of the disease. In certain early stages of the disease it may produce transient temporary remissions, but in advanced stages it is of little or no value and may do harm. Since the infectious nature of the disease is questionable, there seems to be little justification for continuing experiments with fever treatment of this disorder.

NEURITIS

The striking relief from intractable lightning pains in cases of tabes dorsalis obtained by combined fever and chemotherapy led us to treat a variety of painful neuritic and radicular conditions with artificial fever.

Local heat has long been used for relief from pain in peripheral neuritic inflammatory states. Dry heat from electric light bulbs in a cradle placed over painful areas or infra-red lamps has been most commonly employed. Usually, deep tissue penetration of heat by these methods is hard to obtain. Many physicians have used local diathermy to obtain more efficient local heating. Regardless of the method employed, some relief from pain in the neuritides is generally obtained. We are not aware of general artificial hyperpyrexia having been employed extensively in the manner in which we have applied it to obtain relief from pain in neuritis.

Up to Jan. 1, 1937, 40 patients underwent artificial fever treatments in an attempt to obtain relief from severe neuritic, myalgic or radicular painful states.

These patients have been classified as follows: (1) sciatic neuritis, 20 patients; (2) brachial neuritis, 6 patients; (3) toxic-infectious polyneuritis and infective neuronitis, 5 patients; (4) herpes zoster, 3 patients; (5) lymphocytic meningitis, 2 patients, and (6) miscellaneous arthritic states with secondary neuritis or neuralgia, 4 patients.

General Conclusions.—The prompt and striking relief obtained in the majority of patients leads us to believe that artificial fever therapy offers a helpful means of alleviating these states. We have not seen such uniformly favorable response from previously tried therapeutic agents.

The physiologic mechanism of induction of general fever in effecting relief from neuritic pain is not well understood. Undoubtedly, the increased blood flow and peripheral vasodilatation in the inflamed areas increase tissue oxidation and nutrition. The factors of leukocytosis, phagocytosis and mobilization of immune bodies secondary to induced fever play a part in the absorption of rheumatic deposits, dilution of toxins and healing of inflamed nerve tissues.

While we have seen evidence in patients with severe polyneuritis of shortened convalescence, improvement in the blood picture and gain in weight and strength, we cannot definitely attribute these changes to fever therapy. We believe, however, that its use in relieving neuritic pain is, with other therapeutic agents, a valuable aid in treatment. These treatments are well tolerated and are usually welcomed by the patient, since the pain disappears as soon as the body temperature is elevated. The treatments do not interfere with any other therapy indicated and are practically without danger in experienced hands.

Summary of Results.—The treatments are given at temperatures of from 103 to 104 F. for from two to four hours each; from 2 to 6 treatments are given. All types of neuritic pain are relieved immediately, but pain recurs in some conditions, especially in the secondary neuritides resulting from compressive lesions. Fever therapy is recommended not to replace other accepted forms of therapy for neuritis but only to aid in the management of the disease. It probably hastens convalescence in the severe toxic-infectious polyneuritic states.

Of 20 patients with sciatic neuritis, pain was relieved in 80 per cent by combined fever therapy and epidural injections. Patients (20 per cent) who showed no relief had the compressive type of the disease.

In 3 of 6 patients with brachial neuritis there was relief from pain and stiffness of the muscles and joints as a result of fever therapy alone.

In 4 patients with toxic-infectious polyneuritis and 1 with infective neuronitis, all of whom were suffering from severe neuritic or radicular pain, complete relief from pain and hyperesthesia followed fever therapy. The general condition of the

patients improved, and convalescence seemed hastened. Vigorous vitamin therapy was also used in these cases. Details of this study have recently been reported on.[15]

In 3 elderly persons (over 60) suffering from herpes zoster with severe radiculitis complete and prompt relief from pain occurred after from 2 to 3 fever treatments.

In 2 patients with benign lymphocytic meningitis artificial fever therapy seemed to give striking relief from meningitic and radicular symptoms. The general condition of the patients improved with the therapy, and improvement in pathologic findings in the spinal fluid occurred after each fever session.

In 4 patients with arthritic disease accompanied by secondary neuritic or neuralgic painful states marked relief from pain was obtained by fever therapy.

I recommend physically induced artificial fever as a safe, efficient means of relieving neuritic and radicular painful disorders.

CHRONIC MENINGOCOCCIC INFECTIONS

The value of artificial fever therapy for gonococcic infections is well established. Sustained temperatures of from 106.5 to 107 F. destroy at least 90 per cent of strains of gonococci within a few hours.

The morphologic and biologic similarity between gonococci and meningococci led us to experiment on meningococci with thermal death times. Also, an isolated clinical case of meningococcic meningitis in which there was apparent cure after high fever following an intravenous febrile shock reaction further increased our interest in the possible clinical application of fever therapy to chronic meningococcic infections.

In a study of 60 strains of meningococci we found that these organisms react to sustained temperatures in much the same manner as gonococci. Over half the strains died at water bath temperatures of from 41.4 to 41.6 C. (106.5 to 106.8 F.) within eight hours. These results for the thermal death time have recently been confirmed by Moench.[16]

My associates and I reported [17] on the results of fever therapy alone in 2 patients with chronic meningococcemia who were completely cured. We treated 4 patients with chronic meningococcic meningitis; there was clinical improvement, but not cure, from fever therapy alone. The value of this treatment has also been confirmed in the report of a case by Platou, McEmeel and Stoesser.[18]

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15. Bennett, A. E., and Cash, P. T.: The Relief of Neuritic Pain by Artificial Fever Therapy, Arch. Phys. Therapy **19**:69 (Feb.) 1938.

16. Moench, L. M.: A Study of the Heat Sensitivity of the Meningococcus in Vitro Within the Range of Therapeutic Temperatures, J. Lab. & Clin. Med. **22**:665 (April) 1937.

17. Bennett, A. E.; Person, J. P., and Simmons, E. E.: Treatment of Chronic Meningococcic Infections by Artificial Fever, Arch. Phys. Therapy **17**: 743 (Dec.) 1936.

18. Platou, E.; McEmeel, E., and Stoesser, A.: Artificial Fever Treatment of Meningococcus Infections, Minnesota Med. **19**:781 (Dec.) 1936.

We recommend further clinical trial of this method in the treatment of subacute or chronic meningococcic infection, especially meningitis which does not respond to serum or drug therapy. We believe that in acute fulminating types of meningitis fever therapy is contraindicated.

ACUTE INFECTIOUS CHOREA

Fever therapy is rapidly proving to be the most satisfactory method of shortening an attack of Sydenham's chorea and of removing the signs of activity in rheumatic fever.[19] Sutton and Dodge[20] first reported encouraging results from febrile shocks induced with typhoid vaccine. Many workers with physical fever therapy (Schnabel and Fetter,[21] Barnacle, Ewalt and Ebaugh,[22] Neymann and his associates[23] and Desjardins and Popp,[24] and others) have established beyond doubt the superiority of this method.

The University of Colorado group has collected the largest series of cases in which artificial fever was made. A recent summary of these cases follows.

Of 57 patients, 45 recovered completely, and 12 improved markedly; there were 6 recurrences; 4 of these patients received two courses of fever therapy. The average duration of the disease under this treatment was twenty-two and three-tenths days. The average number of treatments was 12.6.

Results in Our Group.—We have treated 8 patients, 1 with a mild, 5 with a moderate and 2 with a severe type of acute infectious chorea. These patients received an average of 9 treatments for from two to three hours at a temperature of 105 F. every day or every other day. All were children except 2 girls, aged 18. Six recovered completely, and 2 showed moderate improvement. One patient had a relapse and returned for a second course of fever therapy. One patient with moderate improvement obtained complete relief from choreic movements after tonsillectomy. The incidence of carditis in the group was about 50 per cent. Carditic complications are not a contraindication to fever therapy.

TOXIC-INFECTIOUS PSYCHOSES

We have treated 5 patients with states classified as toxic-infectious psychoses by means of artificial fever therapy.

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19. Simmons, E. E., and Dunn, F. L.: Fever Therapy in the Treatment of Acute Rheumatic Fever, Tr. Internat. Conf. Fever Therapy **1**:66, 1937.

20. Sutton, L. P., and Dodge, E. G.: The Effect of Fever Therapy on Rheumatic Carditis Associated with Chorea, J. Pediat. **6**:494 (April) 1935.

21. Schnabel, T. G., and Fetter, F.: Fever Therapy in Gonorrheal Arthritis and Chorea, Ann. Int. Med. **9**:398 (Oct.) 1935.

22. Barnacle, C. H.; Ewalt, J. R., and Ebaugh, F. G.: Artificial Fever Treatment of Chorea, J. A. M. A. **109**:111 (July 10) 1937.

23. Neymann, C. A.; Blatt, M. L., and Osborne, S. L.: The Treatment of Chorea Minor by Means of Electropyrexia, J. A. M. A. **107**:938 (Sept. 19) 1936.

24. Desjardins, A. U., and Popp, W. C.: Our Experience with Fever Therapy, Proc. Annual Fever Conf. **5**:7, 1935.

The patients all presented marked confusion and other profound sensorial reactions. One patient with an organic psychosis had associated acute excitement. The other 4 patients presented mixed pictures of apprehensive or suspicious ideas, hallucinatory features, dilapidation in personal habits and clouding of the sensorium. While manic or schizophrenic features could be detected, the essential type of reaction in all cases was that of subclinical delirium.

All patients presented definite evidence of low grade infection, as shown by leukocytosis, rapid sedimentation of the red blood cells, slight fever or physical signs of foci of infection. In 3 patients foci of infection were removed prior to artificial fever therapy without definite improvement in the organic psychotic reactions. In 1 patient with acute pelvic inflammatory disease from induced abortion, salpingectomy performed after fever therapy apparently relieved a state of acute excitement and confusion. One patient had systemic syphilis and associated mental confusion. Complete recovery occurred in all cases.

The treatments consisted of induction of artificial fever for from three to five hours at a temperature of from 105 to 106 F., in from 2 to 6 sessions at intervals of from three to five days.

We recognize that a condition of this type tends to have a good prognosis. It was our impression, however, that fever therapy markedly shortened the usual period of hospital treatment. Our results are sufficiently encouraging to suggest that fever therapy may have a place in the treatment of toxic-infectious delirious states by increasing the patient's resistance to infection. We believe that further experimentation in this field is indicated.

The following case history is an illustration of the type of disease treated.

B. H., a grocer, aged 54, was admitted to the psychiatric department because of marked failure of memory, confusion, neglect of business and untidiness in personal habits. For a number of months he had been drinking steadily each day. Gradually he became shiftless, disoriented, uncooperative and careless with excreta. In the past ten years he had had three operations on the nose for removal of nasal polyps resulting from chronic sinusitis.

Mental Status.—The patient was uncooperative, almost mute and vacuous. For weeks forced feeding was required and the patient was incontinent and untidy. Sensorial tests showed complete disorientation, marked failure of memory and complete lack of insight.

Physical Status.—Polypoid degeneration was present in the nasal fossae; there was cloudiness of all the sinuses, with dental caries and chronic infection of the tonsils.

Laboratory studies revealed normal spinal fluid; the white cells of the blood numbered from 9,000 to 11,000, with 75 per cent polymorphonuclear cells; the blood sedimentation rate was 24 mm. in forty-five minutes. At times there was elevation in temperature of from 1 to 2 degrees F.

Progress.—Six weeks after admission the patient had shown no appreciable improvement in mental status, although the dental infection and tonsils had been removed and radical operative procedures on the sinuses and nose had been carried out to remove all possible foci of infection. The patient had no recollection of these surgical procedures, although they were performed under local anesthesia.

After recovery from the operative procedures the patient was given 2 fever sessions of five hours each, at temperatures above 105 F. After the first treatment improvement in his behavior in the ward was noted; after the second treatment the patient rapidly became alert and interested and showed normal sensorial

reactions, with full insight. Twelve days after the second fever session the blood sedimentation rate had dropped to 24 mm. in four hours. The patient was dismissed as clinically cured twenty-seven days after the first fever treatment. He had complete amnesia for the first eight weeks of treatment. He has maintained normal mental health for three years.

MISCELLANEOUS NEUROPSYCHIATRIC DISORDERS

Functional Psychosis.—We have treated patients with a variety of other psychotic states—agitated, excited and stuporous—to determine whether results can be obtained and to compare the group as a control with the organic toxic-infectious group. Our results have been disappointing. No patient has shown improvement that could be attributed to fever therapy. In this group there were: 1 patient with very acute manic excitement, 4 patients with depressive reactions, 1 patient with characteristic schizophrenia and 1 with psychoneurosis. Three of the patients have fully recovered, but the course of the psychosis was that expected. We did not believe that fever therapy altered the course. At times temporary benefits were observed, probably to be explained by psychic shock.

Lobar Sclerosis.—One patient with the clinical picture of Pick's disease was submitted to 6 fever sessions of five hours each, at temperatures above 105 F. A gain in weight of 15 pounds (6.8 Kg.) followed, but there was no improvement in the profound sensorial defects.

Epidemic Encephalitis.—We have given 6 patients suffering from severe parkinsonian sequelae of epidemic encephalitis 6 heatings of five hours each at temperatures above 105 F., or thirty hours of fever. No objective improvement has been observed in this group. We do not believe that further experimentation with fever therapy is indicated in this group.

Cerebral Arteriosclerosis.—This group consisted of only 4 patients: 1 had an organic convulsive state; 1, paralysis agitans; 1, senile psychosis, and 1, cerebellar degeneration. The results for this group may be dismissed with the statement that we have observed no objective improvement from fever therapy in any of these patients.

CONCLUSIONS

1. Fever therapy in cases of neuropsychiatric disease has become a valuable aid in the cure of many previously hopeless conditions.

2. The choice of methods for production of fever is still in dispute. The cumulative weight of evidence indicates that fever alone is the beneficial agent. Future investigations will finally determine whether the method of choice for the induction of fever is biologic, infectious or physical.

3. Combined artificial fever and chemotherapy appears to have certain advantages over malarial therapy in the treatment of resistant asymptomatic and severe clinical grades of neurosyphilis.

4. Fever therapy is of doubtful value for multiple sclerosis.

5. In obtaining relief from pain in severe neuritic disturbances artificial fever seems a promising aid.

6. For chronic meningococcic infections fever therapy may be curative.

7. Artificial fever appears to be the best treatment now available for shortening the course of infectious chorea and other manifestations of the rheumatic state.

8. Experiments in treating toxico-infectious psychotic states indicate that fever therapy may shorten convalescence.

9. For such disorders as cerebral arteriosclerosis, functional psychoses and chronic encephalitic states fever therapy is of no value.

ANTICONVULSIVE ACTION OF VITAL DYES

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At different times during the past ten years the problem of cerebral anoxemia and its relation to certain convulsive phenomena has been studied in the laboratories of the department of neuropathology of the Harvard University Medical School.[1] A search was begun in 1935 for a stain which might act as an indicator of slight and early asphyxial changes in the nerve cells of the brain and spinal cord. It was observed that neutral red, injected intraperitoneally into mice, could be seen in the ventral horn cells of the spinal cord. This observation was definite, though rare. Asphyxia of the mice with nitrogen caused no increase in the amount of dye taken up by the ventral horn cells. In order to see the effect of the increased motor activity, we then planned to give the animals convulsant drugs.

Accordingly, a study was begun by one of us (J. N.) in which convulsions were induced in mice after the intraperitoneal injection of neutral red. It was noticed that the dye seemed to have an inhibiting effect on the convulsions in these animals; so the investigation of the vital dyes as anticonvulsants was begun. The purpose of this paper is to report the first steps in this study. Experiments were performed on mice, rabbits and rats to test the effect of vital dyes on drug-induced convulsions. Ten patients with "epilepsy" also were treated with dye.

DYES [2]

Neutral red (Grubler) was used in the studies on mice. This dye is weakly basic. Its formula, according to Conn,[3] is shown in figure 1. It was studied

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From the Department of Neuropathology, the Harvard University Medical School, and the Department of Psychiatry, the Massachusetts General Hospital.

1. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of Cats, Arch. Neurol. & Psychiat. **23**:876 (May) 1930. Lennox, W. G., and Cobb, S.: Epilepsy from the Standpoint of Physiology and Treatment, Medicine **7**:229, 1928.

2. Dyes for this study were furnished by the National Aniline & Chemical Company, New York.

3. Conn, H. J.: Biological Stains, Geneva, New York, Commission on Standardization of Biological Stains, 1936.

by Covell and Scott,[4] who showed that it is taken up slightly by ventral horn cells. This dye has been reported by Wittgenstein and Krebs [5] to produce clonic movements in animals.

Brilliant vital red (Evans) was used in all the other studies. It is an acid dye, with the formula, according to Conn,[8] as shown in figure 2. Its staining properties were described by Smith,[6] who showed that it is taken up chiefly by lymph nodes, particularly the reticuloendothelial cells, and also by the convoluted tubules of the kidneys and by elastic tissue. No data on the staining of the nervous system by this dye were available. It has been used extensively in determinations of blood volume, following the method of Keith, Rowntree and Geraghty,[7] and is relatively nontoxic.

EXPERIMENTAL STUDIES ON RATS, MICE AND RABBITS

A. Studies on Mice.—Three convulsant drugs were used: triphenylphosphite, camphor liniment U. S. P. and picrotoxin.

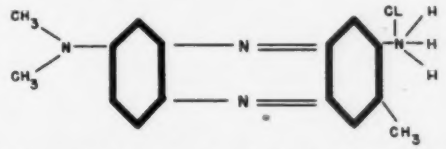

Fig. 1.—Chemical formula for neutral red (aminodimethylaminotoluphenazonium chloride).

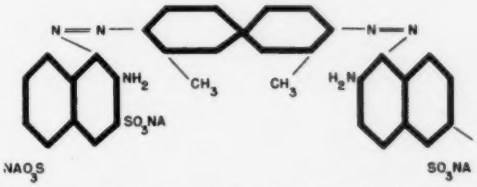

Fig. 2.—Chemical formula for brilliant vital red (tolidine + 1 mol of β-naphthylamine-3, 6-disulfonic acid + 1 mol of β-naphthylamine-6-monosulfonic acid).

The first convulsant used was triphenylphosphite; its properties have been described by Smith, Lillie, Elvove and Stohlman.[8] The pathologic results of large doses in rats include degeneration of tracts in the brain and spinal cord and degeneration of the ventral horn cells.

4. Covell, W. P., and Scott, G. H.: An Experimental Study of the Relation Between Granules Stainable with Neutral Red and the Golgi Apparatus in Nerve Cells, Anat. Rec. **38**:377, 1929.

5. Wittgenstein, A., and Krebs, H. A.: Die Abwanderung intravenös eingeführter Substanzen aus dem Blutplasma, Arch. f. d. ges. Physiol. **212**:268, 1926.

6. Smith, H. P.: The Fate of Intravenously Injected Dye, Bull. Johns Hopkins Hosp. **36**:325, 1925.

7. Keith, N. M.; Rowntree, L. G., and Geraghty, J. J.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547 (Oct.) 1915.

8. Smith, M. I.; Lillie, R. D.; Elvove, E., and Stohlman, E. F.: The Pharmacologic Action of the Phosphorus Acid Esters of the Phenols, J. Pharmacol. & Exper. Therap. **69**:78, 1933.

Experiments were conducted over periods of twenty-four hours. Two cubic centimeters of freshly made 1 per cent neutral red in physiologic solution of sodium chloride, at 37.5 C., was injected intraperitoneally into 20 mice. Twenty additional mice were used as controls. Twelve minutes after injection of the dye into the test animal, 0.1 cc.[9] of triphenylphosphite was injected subcutaneously. The mice used as controls received similar injections of triphenylphosphite. Within from thirty to sixty minutes violent, generalized clonic convulsions occurred, which usually persisted until the animal died. The experiment was carried out over a period of twenty-four hours.

The results (table 1 A) show that the average time of onset of convulsions was delayed in animals with dye and that the survival time of these animals was prolonged. Also, it is of note that only 8 animals survived, 7 of which received dye. The only mouse to survive that did not receive dye was still paralyzed at the end of twenty-four hours.

An experiment was then performed to determine whether the protecting property of neutral red against triphenylphosphite was that of dilution. Twenty-

TABLE 1.—*Results of Injection of Neutral Red in Mice Given Triphenylphosphite*

	No. of Mice	Convulsant	Intravital Dye	No. of Mice with Fits	Average Time of Onset of Fit, Min.	Average Survival, Min.	No. Died	No. Normal at End of 24 Hr.
			A					
Experiment 1	20	Triphenylphosphite	None	20	48	188	19	0
	20	Triphenylphosphite	Neutral red	20	123	245	13	7
			B					
Experiment 2 A	8	Triphenylphosphite	None	6	...	...	4	3
Experiment 2 B	8	Triphenylphosphite	Neutral red	4	...	...	2	3
Experiment 2 C	10	Triphenylphosphite	Physiologic solution of sodium chloride	10	...	...	7	1
Experiment 3 D	3	Triphenylphosphite (mixed in vitro)	Neutral red	3	2	60	3	0

six mice were used in this study (table 1 B). Eight (group A) were given an injection of 0.06 cc. of triphenylphosphite subcutaneously. Eight received injections of 2 cc. of 1 per cent neutral red in physiologic solution of sodium chloride. Fifteen minutes later these animals (group B) were given subcutaneous injections of 0.06 cc. of triphenylphosphite. Ten animals were given intraperitoneal injections of physiologic solution of sodium chloride at 37.5 C. Fifteen minutes later they were given subcutaneous injections of 0.06 cc. of triphenylphosphite (group C). Of group A, 6 mice had convulsions and 4 died; of group B, 4 had convulsions and 2 died; all of the mice of group C had convulsions, and 7 died.

The results indicate that solution of sodium chloride alone has no protecting effect against triphenylphosphite. The mortality was higher for animals which received the solution of sodium chloride and triphenylphosphite than for those which were given triphenylphosphite alone. Those given dye and triphenylphosphite had the lowest mortality.

9. The dose of triphenylphosphite varied in the different experiments, as it deteriorates rapidly and the lethal dose must be assayed for each experiment. The drug was obtained from the Eastman Kodak Co., Rochester, N. Y.

A further experiment was performed to determine whether the protective action of neutral red was due to physical or to chemical union with triphenylphosphite. Two cubic centimeters of neutral red was mixed thoroughly, in vitro, with 0.06 cc. of triphenylphosphite at 37.5 C. for thirty minutes and injected intraperitoneally into each of 3 mice. In these 3 mice convulsions occurred within two minutes and death within an hour (table 1 B). This limited experiment suggests that the protective effect is not one of chemical union of the dye and triphenylphosphite.

The second convulsant used was camphor liniment; experiments were conducted over twenty-four hours. Ten mice serving as controls were given subcutaneous injections of 0.07 cc. of camphor liniment. The second group of 10 mice was given intraperitoneal injections of 2 cc. of 1 per cent neutral red in physiologic solution of sodium chloride. Fifteen minutes later 0.07 cc. of camphor liniment was injected subcutaneously. The results in table 2 show that the onset of convulsions was postponed for forty-five minutes in the animals that had received dye. The average time of onset after injection in the mice without dye was fifteen minutes; in those with dye it was sixty minutes. The occurrence of convulsions, however, and the mortality were not significantly affected.

TABLE 2.—*Results of Injection of Dye in Mice Given Camphor Liniment U. S. P. and Picrotoxin*

No. of Mice	Convulsant	Intravital Dye	No. with Fits	Average Time of Onset of Fit, Min.	Average Survival, Min.	No. Died	No. Normal at End of 24 Hr.
10	Camphor liniment	None	9	15	..	1	4
10	Camphor liniment	Neutral red	8	60	..	0	5
18	Picrotoxin	None	18	1+	..	4	14
18	Picrotoxin	Neutral red	18	1+	..	13	5

Picrotoxin was the third convulsant used. Experiments were conducted over twenty-four hours. Thirty-six mice were employed. Picrotoxin, in doses of 0.007 mg. per gram of mouse, was injected subcutaneously into 18 mice serving as a control group. Two cubic centimeters of 1 per cent neutral red in physiologic solution of sodium chloride was injected intraperitoneally into 18 mice. Fifteen minutes later the same amount of picrotoxin as that in the control group was injected subcutaneously. Convulsions came on immediately in both groups. The results of this study (table 2) show that 13 of the animals which had received neutral red died, as compared with 4 of the group used as a control; so the mortality was materially higher in mice that had received dye than that in the control group; convulsions were equally severe. Histologic studies were made of the brain and spinal cord of several of the mice stained with dye. Fresh preparations, examined by smear or frozen section technic, were the only ones that showed deposits in the nerve cells. These were observed rarely, but appeared always to be in large motor cells of the spinal cord or cerebrum.

Conclusions: 1. The onset of convulsions was delayed in animals given dye when triphenylphosphite or camphor liniment was used as a convulsant. 2. The mortality in animals with dye was lower than that

in animals used as controls when triphenylphosphite was used as a convulsant. 3. The mortality in animals with dye was higher than that in mice used as controls when picrotoxin was used as a convulsant.

B. Studies on Rabbits.—For each of a small series of rabbits the threshold convulsive dose of camphor liniment was determined by injections repeated at intervals of two or three days. Each animal was then given repeated intravenous injections of brilliant vital red in 1 per cent solution until the scleras, the skin and the mucosas became conspicuously red. The convulsive dose of camphor liniment was then given and the result noted. Convulsions with camphor liniment usually occurred within one or two minutes after the injection. A late convulsion was said to be one that occurred after five or ten minutes. In the typical convulsion the rabbit first went into tetanic spasm, with the shoulders high and the head and neck pulled in, from this position breaking into a severe clonic convulsion, all the extremities being involved. A mild convulsion was defined as one in which the animal merely became stiff for a few moments or hunched the shoulders back and gave one or two jerks, but had no severe, sustained clonic movements. Rabbit 6 had no convulsions after the first three injections of brilliant vital red. Rabbit 9 showed a decrease in the severity of convulsions after small doses, but did not cease having convulsions until a large dose, of 30 cc., of the dye was injected. Rabbits 10 and 11 experienced no inhibiting effect from the preliminary injection of the dye, but stopped having convulsions after large doses (30 and 29 cc., respectively) of a 1 per cent solution. Rabbit 12 showed less convulsive reaction after small doses of dye. Rabbit 13 reacted much like rabbit 9.

Histologic studies were unsatisfactory with ordinary technics, as the dye washed out during fixation of the tissue. Rabbit 9 was killed one day after the last intravenous injection of brilliant vital red. Preparations of the nervous system were examined in Ringer's solution while fresh. In the region of the motor cortex one pyramidal cell was seen in which a number of small black dots appeared, which were more numerous around the nucleus than elsewhere. Purkinje cells showed no dye. The only dye observed in the cerebellum was that in the blood vessels. One cluster of eight large nerve cells, apparently ventral horn cells, and another similar single cell were observed all of which contained large red deposits, rather round and about the size of a nucleus. There were also small particles in the cells which stained more yellowish red. No conclusion could be drawn from this inadequate histologic examination.

Other rabbits stained with brilliant vital red have been studied by Cobb, Osgood and Cohen.[9a] Examination of fresh tissues, frozen sections and sections fixed with various fixatives all revealed no dye in nerve cells or glia cells. The choroid plexus, pia-arachnoid and perivascular spaces of the brain, however, showed definite red staining.

All rabbits after being thoroughly stained with brilliant vital red manifested resistance to the convulsive action of camphor liniment (table 3).

A second experiment was conducted on rabbits, using cocaine in a 2 per cent solution as the convulsant.[9b] Cocaine convulsions occur almost immediately

9a. Cobb, S.; Osgood, R., and Cohen, M. E.: To be published.

9b. Brain, R. W.: The Nervous Symptoms of Insulin Hypoglycaemia in Rabbits Contrasted with the Convulsions Induced by Cocaine, Quart. J. Exper. Physiol. **16**:43, 1926.

after injection and are usually definite. The minimal convulsant dose for each rabbit was determined by trial; a dose which produced a definite convulsion on at least five consecutive test days was considered standard for that animal. In rare instances the animals used as controls failed to have a convulsion with this standard convulsant dose (table 4), but there was no evidence of increased tolerance.

To rabbits thus standardized, brilliant vital red was given intravenously in doses indicated in table 4. Only the presence or absence of convulsions was

TABLE 3.—*Convulsive Reaction Before and After Intravenous Administration of Brilliant Vital Red*

Rabbit No.	Weight, Lb.	Dose of Camphor Liniment, Cc.	April 8	10	11	13	15	16	17	21	22
6	3¼	0.25	Fit	8*	10	5	No fit	10	No fit	36	No fit
9	2½	0.25	Fit	5*	5	5	Late fit	9	Late fit	30	No fit
10	3	0.30	Fit	5*	5	5	Fit	10	Fit	30	Slight, short fit
11	2¾	0.35	Fit	5*	5	5	Fit	..	Fit	29	No fit
12	4	0.55	....	..	..	Fit	5	10	Very slight fit	30	..
13	3½	0.40	....	..	..	Fit	5	10	Slight fit	40	No fit

* Figures for this day and subsequent days indicate the dose of brilliant vital red, expressed in cubic centimeters of a 1 per cent solution.

TABLE 4.—*Effect of Administration of Brilliant Vital Red on Cocaine Convulsions in Rabbits*

Rabbit		Cocaine, Convulsive Dose, Mg.	Dye, 2% Solution, Cc.	Convulsions (Before Dye)			Convulsions (After Dye)			Deaths
No.	Weight, Kg.			Trials	Convulsions	%	Trials	Convulsions	%	
101	1.9	12	20	6	6	100	*	..	..	Dye
102	2.2	12	160	6	6	100	10	12	83	
103	1.7	11	20	6	6	100	*	..	..	Dye
104	1.9	12	90	7	7	100	4	5	80	
105	1.8	9.6	163	11	11	100	9	12	75	
106	1.9	13	0	19	21	90	..	..	..	
107	1.8	10.4	75	13	14	93	4	8	50	
108	1.8	10	40	9	11	82	3	3	100	Dye + cocaine
109	1.8	10	0	8	8	100	..	..	..	
110	2.0	12	0	8	8	100	..	..	..	
Total.....				93	98	95	30	40	75	3

* Animal died after injection of dye and before being tested for convulsions.

noted; the severity or the time of onset of the convulsion was not recorded. Two rabbits died within twenty-four hours after receiving the first dose of brilliant vital red; the cause of death was unknown. In table 4 it can be seen that 4 animals had fewer fits and 1 had more after administration of the dye. When all convulsions are totaled, it is seen that the animals used as controls had 93 of 98 convulsions, or 95 per cent, and the animals with dye, 30 of 40, or 75 per cent.

This study suggests a slight protective influence of brilliant vital red against cocaine convulsions.

C. Studies on White Rats.—Dr. A. E. Rauh,[10] working at the Harvard University Medical School, undertook experiments with strychnine. He gave to 12 rats doses of strychnine sulfate sufficient to produce spontaneous convulsions. All these animals had convulsions, and all died. Equivalent doses of strychnine were given to 13 white rats after intravenous injection of brilliant vital red. Of the 13 rats, only 3 showed spontaneous convulsions. Seven of the remaining 10 rats showed convulsions when disturbed by such stimulation as pinching the tail. Four of 10 died, and 6 survived (table 5).

It appears from Rauh's work that the convulsive action of strychnine was somewhat inhibited by the intravenous administration of brilliant vital red.

STUDIES ON PATIENTS

Brilliant vital red was given to 10 children with various types of epilepsy. The details concerning each patient are contained in the case reports which follow:

After a preliminary study as a control to find how many fits each patient was having per day, i. e., to obtain a "convulsion level," brilliant vital red was

TABLE 5.—*Results of Administration of Dye to Rats Given Strychnine* *

White Rats	Drugs	Spontaneous Convulsion	Reflex Convulsion	Died	Survived
12	Strychnine alone	12	..	12	0
13	Strychnine; brilliant vital red intravenously	3	..	..	..
10	Strychnine and brilliant vital red intravenously (animal disturbed)	0	7	4	6

* This investigation was made by Dr. A. E. Rauh.

injected intravenously until the patient became red. It was decided that the dye should be administered until the patient seemed improved or until a toxic sign, such as albuminuria, made further injection unwise. In cases in which the nature of the fits or the type of patient prevented his keeping an accurate account of his own spells, special nurses attended him constantly and recorded all fits. In the case of 1 patient with a large number of petit mal attacks daily, special nurses counted the fits during the eight hour period in which he had most attacks.

The dye, which was kept in serum bottles, was sterile and was warmed before injection. The injection could be made safely as rapidly as the dye would flow into the vein. There was no immediate reaction to the dye, and there was no case of definite thrombosis of a vein, despite repeated injections. At the height of the treatment some patients showed red urine with albuminuria (table 6). All showed red stools; one had red tears, and one red dandruff. At the end of the treatment the patients appeared conspicuously red,[11] but later, as the dye faded, the skin resembled that seen after sunburn. The color disappeared completely in two or three months.

10. Rauh, A. E.: Personal communication to the authors.

11. When matched with the standard color tables published by Ridgway (Color Standards and Color Nomenclature, Washington, D. C., The Author, 1912), the patient's skin at the reddest was geranium pink, shrimp pink or alizarin pink.

Follow-up studies were made in most cases by having the patient return to the outpatient department of the Massachusetts General Hospital at frequent intervals. Communications from physicians constituted the follow-up study in the other cases. The family's convulsion count, while not comparable with the data obtained by special nurses, was deemed useful in checking the family's impression of the patient before and after the treatment.

Charts 1 to 10 and the case records show the details for each patient.

In searching for a new dye, it was considered that neoprontosil (disodium 4-sulfamidophenyl-2″-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate) might be tried.

The reasons for its choice were: (1) It is a red dye; (2) it is a diazosulfonated dye, resembling in those features brilliant vital red; (3) it had already been used in human subjects without obvious ill effects, which is not true of most dyes; (4) there is evidence that it may cause acidosis, and since histologic studies on rabbits

TABLE 6.—*Results of Dye Therapy in Patients with Epilepsy*

Case No.	Patient	Age, Yr.	Weight, Lb.	Total Amount of Brilliant Vital Red Injected, Cc.	Fewer Spells (Early*)	Fewer Spells (Sustained†) Dye and Other Medication	Fewer Spells (Sustained) Dye Alone	Fewer Spells (Family's Impression)	Barbiturates Used	Infection	Albuminuria
1	J. L.	14	74½	315	+‡	+	+	+	0	0	0
2	W. K.	7	55½	271	+	+	+	+	+	0	+
3	E. D.	10	82	423	+	+	..	+	+	0	0
4	O. B.	11	86½	1,396	+	+	+	+	0	0	+
5	G. A.	6	40½	889	0**	0	0	0	0	+	0
6	F. D.	16	124	483	+	+	..	+	+	+	0
7	R. C.	8	55	200	0	+	..	0	+	0	0
8	F. G.	3	32¾	115	+	0	..	0	0	0	+
9	T. T.	17	135	335	+	0	..	+	0	0	0
10	S. E.	19	126½	1,043	0	0	..	0	0	0	+

* "Early" means during or immediately after injection of brilliant vital red.
† "Sustained" means longer than one month after treatment.
‡ + indicates diminution of spells.
** 0 indicates no diminution of spells.

did not show that the central nervous system had taken up brilliant vital red, it was thought that the general chemical effect of this drug might be an important factor, and (5) it may be administered orally.

A suitable patient on whom this drug might be tried was transferred from the Monson State Hospital. She was a girl of 13 years. Measles, mumps and an automobile accident in which she is said to have received a fracture of the skull were important in the past history. Seizures, both petit and grand mal, had occurred during the past five years, with occasional biting of the tongue and rare incontinence of urine. A typical attack consisted of a warning cry, motor movements and confusion for several minutes afterward. After the major convulsions there was sometimes unconsciousness for half an hour. During the last year and a half, at the Monson State Hospital, convulsions occurred at a frequency of from 50 to 100 per month. During the last six months, the number ranged from 55 to 100 per month. Physical examination showed that the patient was normal except for thickness of speech, a more pronounced ankle jerk on the left than on the right, and marked response to stroking of the skin. The intelligence quotient was 72.

An attempt was made to learn the number of convulsions per day when the patient was without phenobarbital; on two occasions the drug was removed, and the patient's convulsions increased alarmingly to a level of 7 or 8 per day: with phenobarbital, there were from 1 to 2 seizures per day. Treatment with the new dye, neoprontosil, was started, the doses being raised gradually from 30 to 150 grains (1.95 to 9.75 Gm.) per day. The dye was administered at intervals of four hours night and day. Convulsions gradually diminished, and phenobarbital was discontinued without exacerbation of seizures. Neoprontosil was removed, and the patient had 8 convulsions per day. It was again administered, and there followed a period of sixteen days during which the patient was free from convulsions. The dye was discontinued, and a red placebo capsule was substituted for the neoprontosil; convulsions again increased in number, and the patient became mentally dull and walked unsteadily. With reinstatement of neoprontosil the spells disappeared, and there have been none for the last two weeks.

It is of interest to note that during a period serving as a control, when the patient was having many spells, the p_H of the blood was 7.49; during a sixteen day interval of freedom from convulsions, when neoprontosil was administered, the p_H of the blood was 7.33 (a change from alkalosis to acidosis). The sulfanilamide content of the blood was 3.2 mg. per hundred cubic centimeters at that time. When convulsions increased after withdrawal of neoprontosil, i. e., the period of administration of the placebo, the p_H was 7.51. This suggests that there may be a correlation between the acid-base action of this drug and an anticonvulsant effect, although the entire study has not showed complete correlation. Blood counts and urinalysis, at first made daily and later twice a week during this study covering a period of two hundred and fifty-one days, showed no evidence of agranulocytosis, severe anemia or renal irritation.

Further studies are being made on this patient and on a boy who appears to be similarly benefited. The results in this case and the absence of toxic effects indicate that this drug may have anticonvulsant effects which may later prove to be of therapeutic value.

Summary.—1. Seven of 10 patients showed temporarily some diminution in the number of convulsions coincidental with administration of brilliant vital red.

2. Six patients showed sustained improvement, but in the treatment of 3 of these phenobarbital was also used. The drug had been used before, however, without success.

3. One patient had complete remission of convulsions.[12]

4. Transient albuminuria occurred in 4 patients.

5. No definite harmful complications have yet been noted in any patient.

6. Two patients treated with neoprontosil have shown marked diminution in the number and severity of convulsions, with no harmful complications.

12. Convulsions returned seventeen months later, after an accident with a firecracker.

COMMENT

Material from various sources giving bits of evidence bearing on the anticonvulsive action of two vital dyes has been presented. None of the studies contains enough data for any valid statistical conclusions. Certain interesting features were common to the experiments on animals and the studies on patients. There was no uniformity of response to various convulsant drugs; there was no uniformity of response in various types of patients. Both in rabbits and in patients during the initial period of administration of brilliant vital red there seemed to be an increase in convulsive activity, evidenced by more severe convulsions in rabbits and more convulsions in patients. It was also noted in the rabbits given cocaine and in 2 patients (E. D. and T. T.) that as treatment progressed the subject seemingly "got set" for a convulsion, perhaps had the first movement of it, and then no more. These analogies were striking.

The question of increased tolerance to the convulsant drugs was not completely ruled out as a factor in the rabbits. In patients the question of the psychic effect of this type of treatment has not been, and cannot be, ruled out. Despite the fact that patients were selected in whom emotional elements were considered to play as slight a role as possible, despite the fact that therapeutic suggestion was avoided, the question remains whether improvement was due to psychotherapy, hospitalization or absence from home or parents. In some cases the patients were studied with phenobarbital, the drug being used either during or subsequent to administration of the dye, but the same or a smaller dose was used after administration of the dye; this makes difficult evaluation of the dye therapy. Two of the patients had an infection (abscess of the lung; German measles) during administration of the dye. When the infection improved the number of seizures diminished. The data for these patients obviously were of no value in determining the results of dye therapy, but were included for completeness. It was thought wise to attribute improvement of these patients to disappearance of the infection rather than to the effect of the dye.

Despite the obvious shortcomings of this study, we believe that the fact that four species of animals showed fewer convulsions after the administration of dye makes it important to carry on a study of this problem. The striking improvement in some patients and the apparent harmlessness of the treatment seem to make its trial justifiable, at least in cases of severe epilepsy not responding to other treatment.

As to the mechanism of action, no data are presented. There are only two reports in the literature that may bear on the problem. Kadji and Taylor [13] obtained a seemingly good therapeutic effect on status

13. Kadji, I., and Taylor, C. V.: The Use of Intravenous Methylene Blue in Status Convulsions, Am. J. Psychiat. **94**:1369 (May) 1930.

epilepticus with methylthionine chloride U. S. P. (methylene blue); they concluded that this action is related to an oxidative effect. Urban [14] reported decrease in seizures in epileptic patients after injection of thorium dioxide into the carotid artery. Thorium dioxide and brilliant vital red are both taken up selectively, for the most part, by the reticuloendothelial system.

Further work by Cobb, Chisholm and Cohen [14a] has indicated that "electrical" convulsions are not inhibited in rabbits by brilliant vital red. In contrast, brilliant vital red does inhibit drug, i. e., "chemical," convulsions in rabbits. Since the dye is present in the choroid plexus, pia and perivascular spaces of the brain, it is a reasonable speculation that the dye acts by an effect on the humoral environment of the brain or, to be more specific, by an effect on the passage of the chemical convulsants into the central nervous system. This leads to the further speculation as to the presence of "chemical convulsants" in patients that are helped by the dye. The possibility that brilliant vital red may inhibit passage of necessary substances out of the central nervous system must also be considered.

Further work is in progress along various lines connected with this problem.

CONCLUSIONS

1. Neutral red and brilliant vital red seem to show anticonvulsive action.

2. It is justifiable to try brilliant vital red in treatment of intractable forms of epilepsy.

REPORT OF CASES [15]

CASE 1.—J. L., a boy aged 14, had had convulsions for four years. The patient was one of identical twins, the other also having occasional convulsions. The mother had toxemia of pregnancy while carrying the patient. In 1930 the child suffered a mild injury to the head, without unconsciousness. Six months later the convulsions started; during them he stared straight ahead with the eyes and head turning to the left; he wet himself during many of these attacks. According to the mother, the patient had at least 20 or 30 seizures per day.

Physical examination showed general underdevelopment, the weight being 74½ pounds (33.8 Kg.). Examination of the mental status showed an intelligence quotient of 73 and erratic behavior. Roentgenograms showed a deformity of the skull consisting of a small anterior and a large posterior fossa. A diagnosis of microcephaly and epilepsy was made.

The patient was kept in the hospital and was attended by a special nurse, first for twenty-four hour periods and later for eight hour periods, until a base line was obtained. Then brilliant vital red was injected intravenously, the patient

14. Urban, H.: Ueber den Karotissinusreflex beim Menschen, Deutsche med. Wchnschr. **61**:1597, 1935.

14a. Cobb, S.; Chisholm, J. F., Jr., and Cohen, M. E.: To be published.

15. Complete reports of these cases are to be published in a report of the Child Neurology Research.

being red throughout the treatment. The skin, conjunctivas and mucous membranes all took on a reddish hue. The spells seemed to decrease in number, as can be seen from figure 3.

On discharge from the hospital the patient was still fairly red, and the convulsions were infrequent. He did not wet himself. Gradually the number of spells increased; the patient wet himself again, and at the last follow-up visit, over a year and a half after the initiation of treatment, the convulsions were about as they had been before the administration of brilliant vital red. The urine was normal.

Case 2.—W. K., a boy aged 7 years, had had convulsions for four months. The father had convulsions. At the age of 1½ years the patient fell 15 feet (487 cm.). He showed marked retardation at kindergarten. Four months before

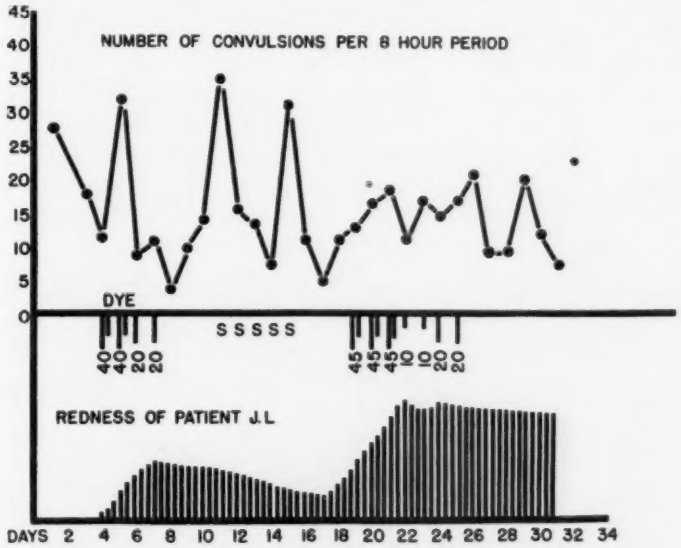

Fig. 3.—Each point on the upper graph represents the number of convulsions from 7 a. m. to 3 p. m. daily, counted by a special nurse. *S* represents the injection of 20 cc. of physiologic solution of sodium chloride.

In this figure and in figures 4 to 10, each point on the upper graph represents the number of convulsions per day, unless otherwise noted. In figures 3 to 12, numbers just below the upper line of abscissas refer to the number of cubic centimeters of 1 per cent brilliant vital red injected intravenously. Lines perpendicular to the lower line of abscissas represent the estimated redness of the patient's skin. These values are not comparable from one patient to another; they indicate merely changes in the individual patient.

administration of the treatment he had the first convulsion, with no apparent cause. The attacks rapidly increased in number. At the Boston City Hospital, under the care of Dr. W. G. Lennox, he was given a ketogenic diet, which somewhat reduced the number of convulsions. Medication with phenobarbital held the number of convulsions at from 12 to 20 per day.

Physical examination showed large tonsils, carious teeth, slight scoliosis and an undescended left testis. The weight was 55½ pounds (25.1 Kg.). The convulsions consisted of extension of one arm, nystagmoid movements of the eyes, a screaming cry and falling to the floor. Mental examination showed feebleminded-ness of a very low level; there were soiling and smearing; the vocabulary was very limited. Behavior was much improved on discharge. A diagnosis of cerebral atrophy, feeblemindedness and epilepsy was made.

After a period as a control, during which the patient was given a constant daily dose of phenobarbital, administration of dye was begun. An attempt was made to discontinue phenobarbital completely during the period of control, but he had convulsions so frequently that it was thought unwise. After administration of brilliant vital red, albuminuria appeared, and at about the same time convulsions diminished and then ceased (fig. 4).

The urine was normal, and the patient had no convulsions until June 1937, when a firecracker exploded in his face. After this, he had about 3 convulsions per week, during which he stared in front of him and clinched his fists.

CASE 3.—E. D., a girl aged 10, had had convulsions for four years. She had exhibited nail biting and temper tantrums in childhood. At the age of 5 years convulsions began with twitching of the mouth and arm on the left side. The patient was observed at a hospital, and a diagnosis of localized convulsions with a questionable etiologic basis was made. The convulsions disappeared until the age of 7, when they reappeared after a Schick test. A ketogenic diet was of definite value. A diagnosis of petit mal was made at that observation at the hospital. One year prior to the time of writing the convulsions had increased again, and on admission the patient was having from 3 to 4 severe convulsions daily, during which she lost consciousness and there were clonic movements of the hands and feet. She continued to grow worse, while taking 2½ grains (0.162 Gm.) of phenobarbital daily.

Physical examination revealed nothing abnormal except obesity. The weight was 82 pounds (37.2 Kg.). Mental examination showed the patient to be good natured, with an intelligence quotent of 86. The urine showed an occasional white cell. The diagnosis was epilepsy and mental retardation.

Phenobarbital was discontinued, and there was a steady increase in the number of convulsions per day. She was then given brilliant vital red, and the number of spells did not decrease. Phenobarbital was then added while the patient was red, and the convulsions immediately dropped to a low level (fig. 5).

The patient returned home, taking daily doses of phenobarbital. For about two months convulsions were practically absent. When they did occur they were slight and all at night; they consisted of a sensation in the left side of the face. As time went on the left side of the face began to twitch, and motor manifestations appeared in the arm. There was no falling. When the patient was last seen (in June 1937) the general health was good, and the number of convulsions varied from none to 2 daily and were still mild, that is, milder than before administration of brilliant vital red but more severe than during the two months following discharge from the hospital. The last examination showed the urine to be normal.

CASE 4.—O. B., a girl aged 11, had had convulsions for eight years. The mother suffered from toxemia while pregnant with the patient. The child talked poorly. At the age of 3 she fell down, screamed and shook slightly. After this, she had many petit mal attacks. At the age of 7, four years before admission,

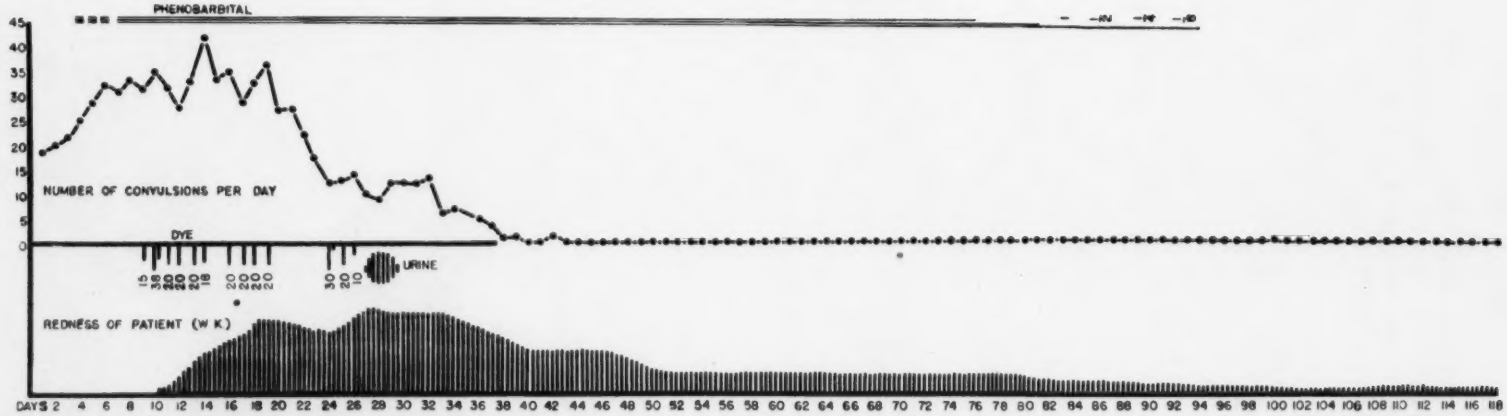

Fig. 4.—Number of convulsions counted by a ward nurse. The broken line at the top represents the intravenous injection of soluble phenobarbital U. S. P., and the continuous triple line, administration of 3 grains (0.194 Gm.) of phenobarbital per day. There is a gradual reduction in dosage, with the dose indicated in grains. The black circle indicates the date of appearance of albuminuria.

she fell, and there was bleeding of the scalp. Two years before admission she entered the Monson State Hospital, where a diagnosis of epilepsy and mental deficiency was made; the intelligence quotient was 32. Records from this hospital stated that the patient had from 495 to 1,287 petit mal attacks a month, while taking ½ grain (0.032 Gm.) of phenobarbital twice a day.

Physical examination showed underdevelopment, slurred speech, almost constant slow, writhing movements of the trunk and head and an equivocal Babinski sign on the right. Convulsions consisted of brief lapses, with blinking of the eyes and jerking movements of the arms and sometimes of the legs. The weight was 82 pounds (37.2 Kg.). Mental examination showed an intelligence quotient

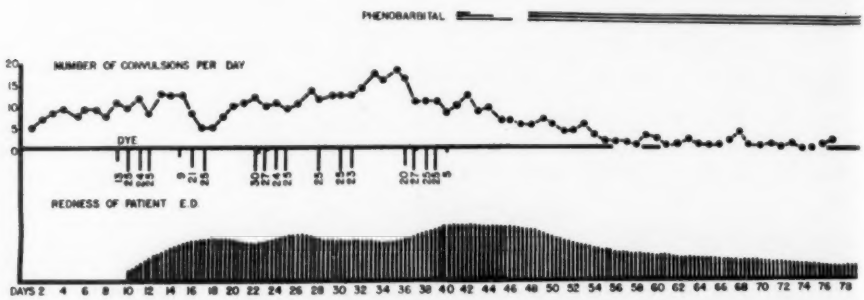

Fig. 5.—Lines at the top indicate administration of phenobarbital per os. The single line indicates 1 grain (0.065 Gm.); the double line, 2 grains (0.13 Gm.), and the triple line, 3 grains (0.194 Gm.) daily. Convulsions were counted by the patient and the ward nurse.

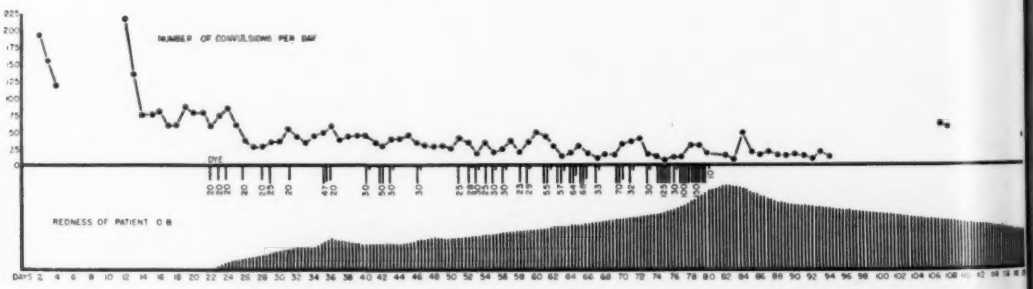

Fig. 6.—The break in the continuity of the graph represents the period when convulsions were not counted by special nurses.

of 30 and extreme docility and affability. Laboratory studies gave normal results except for the appearance of a slight to very slight trace of albumin on occasions during the administration of dye, with the urine clearing completely on discharge from the hospital. A diagnosis of epilepsy and feeblemindedness was made.

After a period serving as a control, the patient was given dye intravenously, and the number of convulsions became less (fig. 6). The general behavior remained unchanged.

A follow-up report, dated February 1937, from the Monson State Hospital, to which the patient was returned, was as follows: "Before treatment with dye the patient had as high as 1,504 spells a month. In other months she had 1,011

and 1,264 attacks. After administration of dye, she had 210 convulsions in September, 419 in October, 412 in December and 389 in January. She has gained weight, but otherwise is about the same. She is very slow to learn. The urine has a specific gravity of 1.023 and is otherwise normal."

CASE 5.—G. A., a boy aged 6, had had convulsions for four years. There was a history of rickets, mumps, contusion of the head, fracture of the right clavicle and scarlet fever. The patient contracted mumps and was sent to a hospital in 1932. While there, he fell from the bed and sustained a contusion of the head. Shortly after, he began to have convulsions, which became increasingly numerous. There was 1 grand mal seizure, but all the others were characterized by falling forward with apparent loss of consciousness. Various types of treatment were tried. The patient, however, continued to have about 15 or 20 convulsions daily, the highest number being 95, according to the count at the Emma Pendleton Bradley Home, where he was being treated.

On transfer to the Massachusetts General Hospital, examination showed undernutrition, a large head with prominent frontal bosses and large tonsils. The convulsions were all alike: The patient doubled up like a jackknife; his head was bent into his lap, and his arms waved in the air above his head. The weight was 40½ pounds (18.3 Kg.). The intelligence quotient was 95. The white blood cell count varied from 7,000 to 20,000, and examination of the urine showed albumin and fine granular casts on two occasions. Roentgenograms of the skull taken in 1933 showed evidence of linear fracture of both parietal bones. An encephalogram at that time showed moderately extensive hydrocephalus with atrophy of the brain, chiefly of the frontal lobes and basal portions. The diagnosis on admission was undernutrition and epilepsy, of unknown cause.

After a period as a control, administration of brilliant vital red was started (fig. 7). The patient had German measles during his stay in the ward, apparently as a result of exposure during transfer to the hospital; in association with this the number of convulsions increased. After the measles subsided the convulsions diminished. He was also receiving more dye at this time. He had two episodes of pain in the calves of the legs and the abdomen during his stay, the nature of which was not understood. On discharge the patient's status was approximately the same as on admission.

The last follow-up study showed that the patient's general condition had remained unchanged and that his color had practically returned to normal.

CASE 6.—F. D., a boy aged 16, had had convulsions for four years. There was a history of chickenpox and measles, with mumps and scarlet fever at the age of 12. The family dated the convulsions from the attack of scarlet fever, in 1932. During an attack, there was a "funny feeling" in the chest, followed by semiconsciousness and gasping for breath, with clonic movements of the arms. The patient was studied in the neuromedical service of the Massachusetts General Hospital in 1934. A diagnosis of idiopathic epilepsy and cortical atrophy was made. The patient had progressed fairly well under treatment with phenobarbital until one month ago, when a tooth was extracted. The number of spells increased; in some attacks unconsciousness persisted for from fifteen to twenty minutes.

On admission, physical examination showed an area of dark pigmentation in the postaxillary line on the right side of the chest. The tonsils were large; the knee jerks were hyperactive, and there was an equivocal Babinski sign bilaterally,

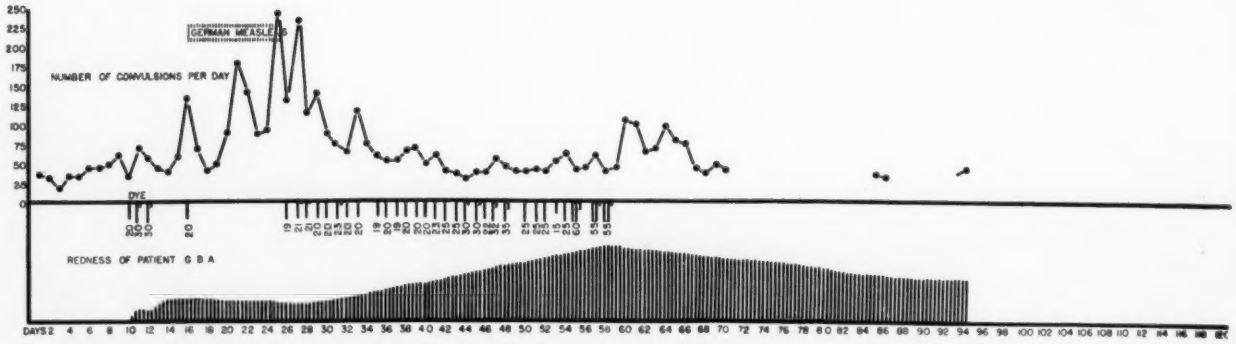

Fig. 7.—The period when the patient had German measles is indicated. The break in the continuity of the upper line indicates the period when convulsions were not counted by special nurses.

more constant on the right. Observation of convulsions showed that the patient knew they were coming; he sat up and folded his arms over his chest; the right arm moved more than the left; the right eye closed and he stared across the room and moaned. The legs were extended and moved restlessly. Speech was thick, choppy and confused. After recovery speech was thick, but understandable. During the latter part of an attack a definite Babinski sign developed on the right. A diagnosis of epilepsy, of unknown cause, was made. The weight was 124 pounds (56.2 Kg.)

A period serving as a control, during which the number of convulsions was counted, was followed by intravenous administration of brilliant vital red (fig. 8). Fever and cough developed. Convulsions increased in number, and further investigation showed that the patient had a small abscess of the lung, probably secondary to extraction of a tooth one month before admission. He had severe coughing spells; one day he coughed up old clotted blood, and the abscess cleared. Frequency of convulsions returned to a low level. The patient was given pheno-

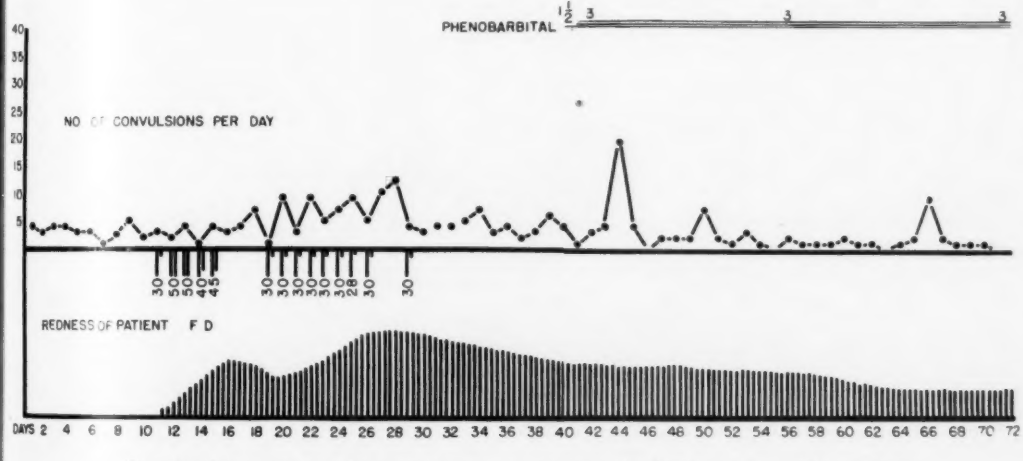

Fig. 8.—Lines at the top indicate the use of phenobarbital per os. The numbers affixed to these lines represent the daily dose, expressed in grains. Convulsions were counted by the patient and the ward nurse.

barbital when the diagnosis of an abscess of the lung was made, and this was continued after discharge. The convulsions now average about 1 per day, with an occasional day on which there is none. Attempts have been made to have the patient adjust socially, and superficial psychotherapy has been tried. When the patient was last seen in June 1937, the general condition was good, and the urine was normal.

Case 7.—R. C., a boy aged 8, had had convulsions for five years. He was born by difficult forceps delivery. At the age of 2½ years he had convulsions, which were chiefly on the right side. They were usually associated with infection of the upper respiratory tract. At the age of 3 encephalograms showed slight enlargement of the ventricles and the subarachnoid space. The following year the patient was readmitted to a hospital because of persistence of convulsions. At that time he was thought to be "mentally inadequate," left handed and right eyed.

Physical examination gave normal results except for frequent convulsions, which were chiefly on the right side, although atypical. Mental examination showed the patient to be overactive, overemotional and combative, with marked reactions of a spoiled child. The nurses asserted that he could call up convulsions voluntarily and did so to avoid unpleasant situations. An encephalogram showed the relative size of the ventricles to be unchanged. A diagnosis of epilepsy, with the question of a tumor or scar of the brain, was made. Convulsions became more frequent, until the patient was having from 10 to 200 per day. The weight was 55 pounds (24.9 Kg.).

Brilliant vital red was administered (fig. 9); there was no decrease in convulsions. The patient became very combative: Treatment with a proprietary hypnotic and anodyne mixture (neurosine),[16] 1 fluidrachm (3.7 cc.) three times a day, decreased the number of spells. Brilliant vital red was administered at the Children's Hospital. The boy was transferred to the Massachusetts General Hospital, where a left osteoplastic craniotomy revealed suggestive atrophy of one sulcus between the motor and the premotor area, at the level of innervation of the hand. The arachnoid was a little thicker than normal, and there was a slight tendency to laking of spinal fluid beneath it.

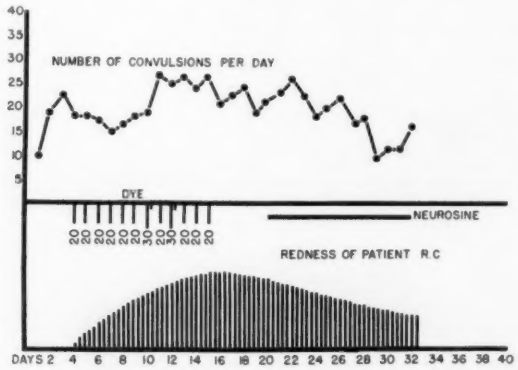

Fig. 9.—Convulsions were counted by the patient and the ward nurse. The black line below the upper line of abscissas represents administration per os of a proprietary hypnotic and anodyne preparation (neurosine), 3 fluidrachms (11.1 cc.) daily.

After discharge the patient was placed in a foster home, and social adjustment and psychotherapy were attempted. He seemed to improve on this regimen. When last heard from, in October 1937, he was having 1 convulsion per week.

Case 8.—F. A. G., a girl aged 2 years and 8 months, had had convulsions for one-half year. The father had migraine; the mother had convulsions, as did many members of her family. The patient's first convulsions occurred at the age of 14 months; after this, she had convulsions with pertussis, measles and the onset of a cold. In February 1936 the patient had 6 generalized convulsions within a few hours. At that time a diagnosis of epilepsy due to degenerative disease was made,

16. Neurosine has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association. It contains about 15 grains (0.9 Gm.) of bromides per fluidrachm.

and a ketogenic diet and phenobarbital were tried, with improvement. Phenobarbital was gradually withdrawn, and the spells returned. Eventually, the convulsions were not controlled by phenobarbital. An encephalogram in March 1936 showed evidence of enlargement of the ventricles and atrophy of the brain. In April 1936 convulsions were right sided, and flaccidity had developed.

Physical examination showed evidence of total blindness, a slight convergent squint and ptosis of the left eyelid. The child was fairly unresponsive. She weighed 32¾ pounds (14.8 Kg.).

Brilliant vital red was administered (fig. 10), after a convulsive level was reached, and there was coincident disappearance of convulsions. Over a period of months convulsions gradually returned, averaging about 1 a day, but there have been occasions when the number rose to 11 per day.

A follow-up visit in December 1937 showed in addition to convulsions, as before, mental retardation and poor vision.

CASE 9.—T. T., a boy aged 17, had had convulsions for eleven years and disturbance in behavior. The maternal grandmother had convulsions. From the age

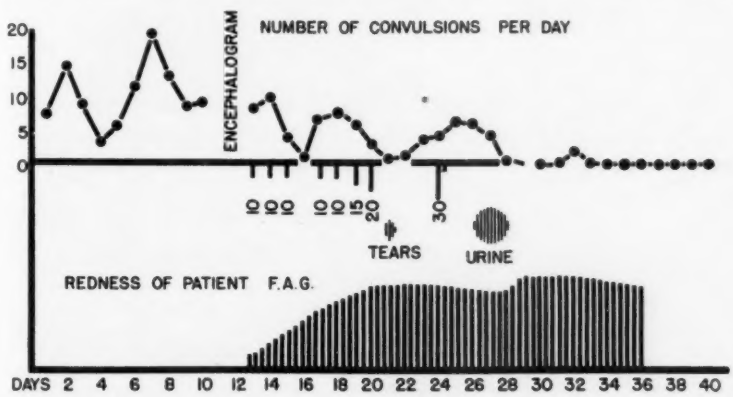

Fig. 10.—The break in the upper graph represents the period of encephalographic examination and accompanying anesthesia. Convulsions were counted by the ward nurse. Appearance of pink tears and albuminuria are indicated by *tears* and *urine* respectively.

of 6 the patient had epileptic equivalents, and at the age of 11 grand mal attacks began, averaging about 1 a week. They consisted of generalized convulsions, with tongue biting, cyanosis, incontinence and unconsciousness. Phenobarbital did not help the patient. Outbursts of temper and unmanageable behavior characterized the picture.

The patient weighed 135 pounds (61.2 Kg.) at the time that a convulsive level was obtained at the Boston City Hospital; red dye was administered there, and this was continued by the local physician after discharge. Figure 11 shows the course of convulsions. After a few weeks, however, the patient continued to have more outbursts of temper; convulsions returned, although not to the same level as before treatment with the dye, and neurosurgical removal of bony projections in the frontal bone was attempted. After this, the outbursts of temper diminished for several months, and convulsions remained at a low level.

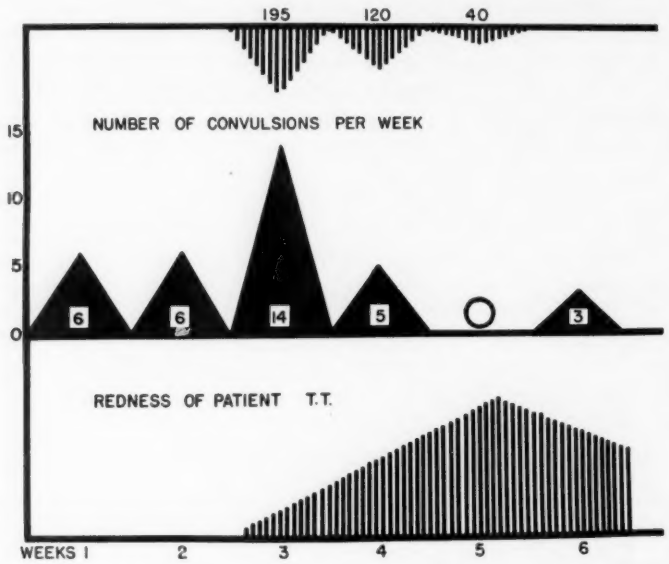

Fig. 11.—Convulsions were counted by the patient, the patient's father and the ward nurse.

In this figure and in figure 12, the number of convulsions per week is indicated by solid black triangles. The number of cubic centimeters of brilliant vital red injected is represented by the shaded triangles at the top of the chart.

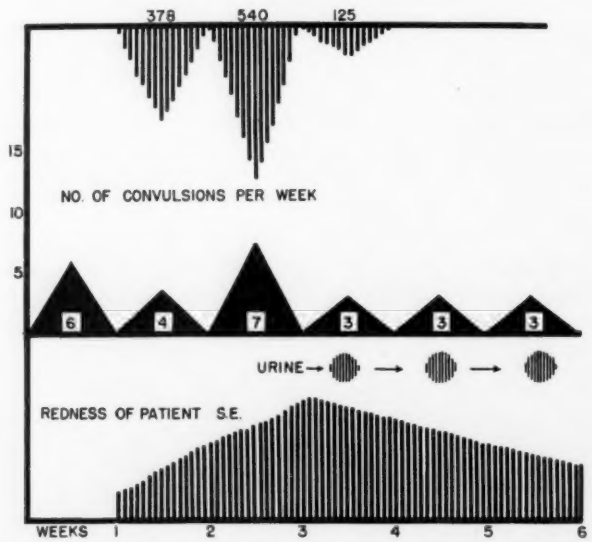

Fig. 12.—Administration of dye is indicated in terms of a 1 per cent solution. However, the dye was actually given in a 2 and approximately a 5 per cent solution. Circles marked *urine* indicate onset of albuminuria.

CASE 10.—S. E., a woman aged 19, had had convulsions for nine years, since the age of 10. The maternal grandmother had migraine, but there was no history of convulsions in the family. At first the attacks consisted of loss of consciousness; then generalized motor convulsions began. A ketogenic diet was beneficial, and the patient became free from convulsions until 1932, when they reappeared and occurred once every two weeks. Phenobarbital seemed to reduce the number and severity of attacks, but there still occurred severe grand mal seizures with periods of mental confusion.

An encephalogram in 1934 showed cortical atrophy, more marked on the right. Craniotomy was performed, and atrophy of the brain and laking of fluid were seen. The patient was not improved by the operation. Mental deterioration progressed. The weight was 126½ pounds (57.4 Kg.).

The patient was admitted for brilliant vital red therapy. Figure 12 shows the course in the hospital; it will be seen that there was no benefit to the patient.

BRILLIANT VITAL RED AS AN ANTICONVULSANT IN TREATMENT OF EPILEPSY

A STUDY OF THIRTEEN CASES

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In 1935, Cobb, Cohen and Ney,[1] searching for a stain which would indicate early asphyxial changes in nerve cells of the brain and spinal cord, observed that when neutral red is injected intraperitoneally into mice the dye in some instances appears in the ventral horn cells of the spinal cord. Asphyxiation by nitrogen did not enhance the affinity of the nerve cells for the dye, but extreme motor activity resulted in greater absorption of dye by the cells. In order to produce such motor overactivity two convulsant drugs, triphenylphosphite and camphor liniment U. S. P., were given to separate groups of mice after intraperitoneal injections of neutral red. Unexpectedly, it was found that the neutral red markedly delayed the onset of convulsions as compared with the time of onset of convulsions in mice which had not received neutral red. Picrotoxin, on the other hand, caused immediate convulsions in both the mice protected by neutral red and those not receiving the dye.

Next, similar experiments were repeated on rabbits, but brilliant vital red was used instead of neutral red. The convulsant threshold dose of camphor liniment was first determined; then brilliant vital red was given intravenously until the rabbits' scleras, skin and mucous membranes became red; finally, the previously determined convulsant dose of camphor liniment was given. All the rabbits exhibited definite resistance to the convulsive action of the camphor liniment, convulsions being either entirely inhibited or reduced in number and severity.

Experiments on the effect of brilliant vital red on strychnine convulsions in white rats was carried out by Rauh,[2] who found that intra-

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1. Cobb, S.; Cohen, E., and Ney, J.: Brilliant Vital Red as an Anticonvulsant, Arch. Neurol. & Psychiat. **37**:463 (Feb.) 1937.

2. Rauh, A. E.: Personal communication to the authors; cited by Cobb, Cohen and Ney.[3]

venous administration of brilliant vital red also somewhat suppressed the convulsant action of strychnine. In 1937 Cobb, Cohen and Ney [1] reported on the anticonvulsant effect of brilliant vital red in experimental animals and man. With this past as a basis, Cobb, Cohen and Ney [3] continued the pioneer work of the therapeutic administration of brilliant vital red to patients with epilepsy. Subsequently, we were encouraged to use the dye in treatment of a group of patients at the Monson State Hospital for Epileptics.

Brilliant vital red is the sodium salt of ditolyldiazo-3, 6-disulfobetanaphthylaminebetanaphthylamine-6-sulfonic acid.

Brilliant vital red is absorbed by the reticuloendothelial cells of the body and, to some extent, by the large motor nerve cells of the brain and spinal cord, as has been shown by experiments on animals.[3] Smith, in his investigation on the fate of intravenously injected brilliant vital red in dogs, observed that "before being eliminated from the body much of the dye is taken up and stored by phagocytes," but that the dye is not completely removed from the plasma "because the phagocytic reaction is a matter of equilibrium between phagocytes and the dye-colored plasma." He also observed that "dye passes in considerable amounts into the lymph." [4]

Excretion of brilliant vital red is largely via the liver. Smith showed that when the bile duct of a dog is cannulated brilliant vital red appears in the bile in relatively high concentration within a few minutes after intravenous injection of the dye.[4] In our cases it was noted that the stools became red within twenty-four hours after the injections of dye were begun. Elimination of the dye by the kidneys occurs in small amount after much dye has been given. This is indicated by the pinkish tinge of the urine and the pink color of some of the dye-stained leukocytes, degenerated cells, granular casts and squamous epithelial cells seen in our cases. Sebaceous, sudoriparous, salivary and lachrimal glands also excrete the dye to a slight extent.

As early as the second day after the first intravenous injection of brilliant vital red the skin of some of our patients began to take on a pinkish tinge. Succeeding injections intensified the color of the skin and the scleras to the point of definite redness. After moderately large amounts of brilliant vital red had been given, it was observed that the optic disks of several patients were noticeably pink. The ear drums of some of the patients were distinctly discolored, resembling in many instances the hyperemia of acute otitis media.

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3. Cobb, S.; Cohen, E., and Ney, J.: Anticonvulsive Action of Vital Dyes, Arch. Neurol. & Psychiat., this issue, p. 1156.

4. Smith, H. P.: The Fate of an Intravenously Injected Dye (Brilliant Vital Red) with Special Reference to Its Use in Blood Volume Determination, Bull. Johns Hopkins Hosp. **36**:325, 1925.

Studies of the spinal fluid were carried out in several cases and will be discussed in a later paragraph.

Basal metabolic rates determined before dye was given and again during the height of administration of the dye were not remarkable, except in case 2. In this case the basal metabolic rate before administration of dye was + 32 per cent and during the height of treatment + 3 per cent.

MATERIAL STUDIED

Our material consisted of 13 institutionalized epileptic boys whose ages ranged from 8 to 16 years. The patients were selected on the basis of the frequency of seizures in the past, without regard to the duration of the disease, history, results of physical examination or age. Boys were chosen because in the boys' building of the children's colony the patients could be kept in a segregated group in a section of the dormitory, dining room and playground and could be closely watched twenty-four hours a day by nurses and attendants.

A preliminary observation period of sixty days was established as a control, during which the patients' convulsions were counted and recorded during twenty-four hours a day. During this period it was found that, although most of the patients had convulsions at fairly frequent or regular intervals, a few had seizures less frequently or at longer and more irregular intervals than we anticipated from examination of the previous monthly convulsion records for each patient. Nevertheless, we continued to include these patients in our study, since we concluded that over a prolonged period of observation during and after administration of brilliant vital red a distinct rise or fall in the total number of convulsions might have significance. The medication, diet and usual daily routine of the patient remained the same during and after the periods of control and administration of dye, except as indicated in the abstracts of the cases. All patients were receiving phenobarbital before dye was given, and the drug was continued as usual during and after the period of administration of the dye, except in case 2, in which the drug was discontinued on Nov. 11, 1937. During the observation period complete urinalyses and determinations of the basal metabolic rate were made several times. The patients were weighed each month, as usual, during both the period of control and that of administration of dye.

A 2 per cent, and later a 1 per cent, solution of brilliant vital red [5] was made with single distilled water and filtered and autoclaved at 15 pounds' (7.5 Kg.) pressure for thirty minutes. A liter of the solution was made at a time; before autoclaving it was divided into several small flasks to facilitate handling.

The dye was slightly warmed and was injected intravenously with moderate rapidity. In this connection, it may be mentioned that, unlike many other medicaments, there seems to be no danger from rapid injection. Neither is it necessary to determine the possibility of allergic reaction. An initial dose of from 10 to 20 cc. was given, and thereafter from 20 to 40 cc., as a rule, from two to four times a week. Exceptionally, a dose of 50 cc. was given.

In determining the optimal dose and frequency of injection of the dye we were governed chiefly by two opposing factors: on the one hand, sufficient amount of dye and frequency of injections to produce and maintain a high concentration of the dye in the body (as indicated roughly by the degree of redness of the skin)

5. The brilliant vital red used in this study was supplied us by the National Aniline & Chemical Company, New York.

and, on the other, avoidance of renal irritation from too frequent or too large injections of dye.

During the entire period of administration of the dye, examinations of the urine were made the morning after an injection and usually also on the morning of each day on which an injection was planned. The first morning specimen of urine was used for examination. Four abnormal urinary findings were encountered at one time or another in all the specimens of urine: (1) albumin; (2) red blood cells; (3) finely granular, degenerated cells, and (4) finely granular casts. Albumin and red cells appeared earliest, often within the first few days or a week of injection of the dye, while the granular cells and casts seldom appeared before the second week. The following factors were our guides in controlling the intervals of and the doses for injection: (1) the physical reaction, (2) the effect on the urinary findings, (3) the patient's behavior, (4) the effect on the number of seizures and (5) the intensity of change in color of the skin. In most instances, during the first month of administration of dye degenerated cells and granular casts in the urine were few; when injections were discontinued for from one to three days they disappeared or became scarce. By the end of two months of treatment, however, moderate or large numbers of these elements were seen in all cases and persisted for longer periods. The presence of albumin and red blood cells, on the other hand, seldom constituted a contraindication to injection of the dye, since, as a rule, they disappeared within from thirty-six to seventy-two hours after interruption of the injections.

Being uncertain as to the pathogenesis and significance of the renal "irritation," we thought it advisable, at the end of about two months (April 19 to 25, 1937), to withhold treatment for several weeks, in order to determine whether the urinary findings were likely to continue, become worse or disappear. At the end of a period of rest of about three weeks (May 14) the abnormal renal elements had almost disappeared from the urine in all but 4 cases. The urinary sediments in 3 of the 4 cases returned to normal two or three weeks later. We have been continually on the watch for signs or symptoms of nephritis. To date, we have no definite clinical or laboratory evidence of permanent renal damage in the 13 patients in our series, as revealed in studies of the blood pressure and eyegrounds, examination for edema, search for symptoms, the Mosenthal and phenolsulfonphthalein tests, nonprotein nitrogen determinations and examination of the urinary sediments.

At the termination of this period of rest, before resuming administration of the dye, we reviewed the apparent effect of the dye on the frequency of convulsions. Four patients (cases 1, 2, 3 and 9) were having much fewer spells; 3 (cases 5, 6 and 12) were having slightly fewer spells, and 6 (cases 4, 7, 8, 10, 11 and 13) were having more spells. The amount of dye thus far administered up to the period of rest ranged from 844 to 1,445 cc. of a 1 per cent solution. In deciding which patients were to continue to receive dye, we concluded that diminution of seizures up to this time did not constitute the sole criterion. The amount of dye given so far had to be considered also in relation to renal "irritation" and unfavorable changes in behavior. Of the 4 patients (cases 1, 2, 3 and 9) who were having fewer spells, 2 (cases 1 and 3) showed only slight evidence of renal "irritation" (a few degenerated cells and no red cells, casts or albumin) at the end of the three week period of rest, and their general condition was good. Therefore, we decided to see whether further administration of dye would reduce still more the convulsions of these 2 patients. In cases 2 and 9 there was still considerable evidence of renal "irritation" at the end of the three week rest period,

but the general condition of the patients was good. In case 9 the urinary findings returned practically to normal two weeks later (May 28), and injections of dye were then resumed to see whether more dye would continue to diminish the number of seizures. The abnormal urinary findings in case 2 persisted for months, and we decided to abandon further injections in this case. The 3 patients who showed only slight decrease in the frequency of spells seemed to be essentially the same in every other respect at the end of the three week rest period, and urinary findings were again nearly normal. Since these patients had received less dye than most of the others, we thought it reasonable to give them more dye to determine what the effect of a materially larger amount would be. Of the 6 patients who were now having more convulsions, we decided to give up further treatment of 4 (cases 4, 8, 10 and 13) because, in addition to the increased number of seizures, they appeared to be deteriorating more rapidly than before, were drowsy and showed more motor incoordination. The other 2 patients of this group (cases 7 and 11) we decided to include for further treatment, since they were large and more dye might be necessary for anticonvulsant effects.

Injections of dye were therefore resumed in 8 cases—in 6 (cases 1, 3, 5, 6, 7 and 11) on May 14, in 1 (case 12) on May 15 and in 1 (case 9) on May 28, with reasonable assurance that the renal changes were transient. At this time we reverted to a 1 per cent solution and used this concentration throughout the rest of the period of administration of the dye. We terminated the injections of dye in cases 6 and 7 on May 18, 1937, in case 11 on May 24, in case 1 on July 7, in case 9 on July 8 and in cases 3, 5 and 12 on July 12.

Untoward transitory effects of a mild nature were noted chiefly during the first month of treatment. After that, the patients rarely had any complaints that we could associate with administration of the dye. All the patients frequently complained of sore eyes and blurred vision for a few hours after injections were given. Increased salivation was noted in 3 patients and continued as long as they received dye and for a few days after the last injection. Frontal headache occasionally appeared in 2 patients immediately after injections and lasted from a few minutes to a few hours. In addition, 1 of these patients was usually dizzy for a few minutes immediately after an injection. Pain in the upper left quadrant of the abdomen was complained of by 2 patients who had been receiving dye for several weeks. The pain came on several hours after each of two injections and lasted about twenty-four hours. No enlargement of the spleen could be felt in either patient. Elevation of temperature, of from 1 to 3 degrees F., occurred in 3 patients in the first week and lasted from twelve to twenty-four hours.

Lumbar punctures were performed on 2 patients (cases 11 and 9) after they had received 1,700 and 1,870 cc., respectively, of a 1 per cent solution of brilliant vital red. The spinal fluid in case 9 was pale, but definitely pink, while that in case 11 presented a faint tinge of pink. In neither case was there an abnormal number or type of cells in the spinal fluid. The total protein content in case 9 was 80 mg. per hundred cubic centimeters of fluid, but this reading may have been inaccurate because of the pink color of the fluid. The total protein content in case 11 was 23 mg. per hundred cubic centimeters of fluid. The dynamics of the fluid in both cases were within normal limits. Three lumbar punctures in 2 other cases, not in this series, performed when the skin was red due to injections of brilliant vital red, may be summarized at this point. In the case of E. E., a girl aged 17 years, who had received the last injection of dye two weeks prior to puncture, examination of the spinal fluid revealed no abnormalities in pressure, dynamics or color. The cytologic reaction, protein and sugar contents, colloidal

gold curve and Wassermann reaction were normal. In the case of P. W., another girl aged 12 years, examination of the spinal fluid two weeks after the last injection of dye also did not show any abnormal changes. Thirty cubic centimeters of 1 per cent solution of the dye was given intravenously, followed three days later by a similar injection of 50 cc. of dye. On the day following the second injection a lumbar puncture was performed. The only abnormality was the faintly pinkish color of the fluid against a white background, as compared with tap water. A benzidine test for blood gave negative results, excluding the possibility that the pink color was due to hemolyzed red cells.

Six patients received the first injection of dye on Feb. 22, 1937, 2 on March 1 and the remaining 5 on March 3. The seizures were recorded from the beginning, as well as after the termination, of administration of the dye, in the same manner as in the sixty day preliminary period. Data on the amount of dye administered, dates of interruption in treatment, termination of administration of dye and effects of treatment on each patient are found at the end of the abstract of each case. The accompanying charts serve as a graphic summary of the effects of administration of brilliant vital red on convulsions during and following the administration of the dye in each case. The number of seizures during the sixty day period before administration of the dye are represented in the extreme left hand box, and the boxes to the right represent the number of seizures in sixty day periods during and after the period of administration of dye. The accompanying table gives a brief summary of the significant data and results in the 13 cases.

REPORT OF CASES

Case 1.—R. W. O., a well developed white boy aged 16, with a mental age of 3 years, who had had both petit and grand mal convulsions since the age of 5½ years, had been at the Monson State Hospital for the past seven years. Since the onset of epilepsy the seizures had become more frequent and severe. The family history was irrelevant.

The past history was irrelevant except for the onset of seizures. In 1930 three dietary regimens were tried at different times: (1) a diet low in sodium, but with the addition of calcium lactate and calcium chloride; (2) a ketogenic diet, and (3) a ketogenic diet with restriction of water. None of these regimens had any appreciable anticonvulsant effect. The patient had taken phenobarbital or bromide since the onset of convulsions.

Physical Examination.—The findings in 1930 were not remarkable. In 1934 the tendon reflexes were hyperactive. In 1935 hyperactive knee jerks and a Babinski reaction were noted bilaterally.

Ventriculographic examination at the age of 10 showed symmetrically enlarged and freely communicating lateral ventricles and no excess of air in the subarachnoid space.

Diagnosis.—The diagnosis was idiopathic epilepsy with mental deterioration.

Medication.—Phenobarbital, ¾ grain (0.048 Gm.), was administered morning and night before and during the study.

Brilliant Vital Red: Administration was begun on February 22, discontinued on April 25, resumed on May 14 and terminated on July 19, 1937. A total of 2,214 cc. of a 1 per cent solution of the dye was given.

Effect on Convulsions.—During the sixty day period before the dye was given the patient had 394 petit mal and 196 grand mal seizures. From the time injections of dye were begun to the present, seizures gradually diminished in number. There

was a steady decline in the number of petit mal seizures. On the twenty-seventh day of administration of dye the patient had 104 grand mal seizures in status epilepticus, which accounts for the unusually large number of grand mal spells in the first sixty day period of dye therapy. Since, grand mal seizures were always less numerous than before the administration of dye, although they varied considerably in number. The sudden predominance of grand mal seizures recorded in the last five months was, we believe, due to change of attendants, who interpreted differently the nature of the patient's convulsions. Before dye therapy the patient "screamed and fought so hard that it was impossible for any one to hold him, in order to prevent his running and hurting himself." At the height of treatment the convulsions were less severe, and the patient did not scream and run around while in a seizure. Soon after termination of administration of the dye the patient again screamed and fought during convulsions.

Renal "irritation," on the whole, was slight.

The general behavior and mentality of the patient were not appreciably affected by the dye.

Case 2.—J. M., an underdeveloped but well nourished white boy aged 11, with a mental age of 10½ years, who had had seizures since the age of 4 years, had many petit mal seizures every day, but rarely a grand mal attack. He had been at Monson State Hospital for two years. The family history was irrelevant.

The patient had an injury to the head at the age of 3½ years, from falling 7 feet (213 cm.), which rendered him unconscious and caused profuse bleeding. The first convulsion occurred six months later. Otherwise, the past history was not significant.

Before admission to the hospital the patient had taken various medicaments for epilepsy, without benefit.

Physical Examination.—The results were normal.

Diagnosis.—The diagnosis was symptomatic epilepsy.

Medication.—Phenobarbital, 1 grain (0.065 Gm.), was administered morning and night before and during the study until Nov. 10, 1937, except from March 16 to April 2, when the dose was doubled because of temporary sudden increase in frequency of seizures during the early part of administration of the dye. Since November 10, use of phenobarbital was omitted.

Brilliant Vital Red: Administration was begun on February 22 and terminated on April 25, 1937. The patient received a total of 1,456 cc. of a 1 per cent solution. No further injections were given because of severe renal "irritation" which persisted for several months after injections were discontinued.

Effect on Convulsions.—In the sixty day period of observation before administration of the dye the patient had 1,819 petit mal and 5 grand mal seizures. Diminution in the number of seizures was most marked in the sixty day period between Dec. 19, 1937, and Feb. 16, 1938, when he had only 2 grand mal seizures. Except for a slight increase in the number of spells in the second week of administration of the dye, there was a striking continual decrease in the number of spells; four weeks after administration of the dye was terminated, the patient was free from attacks for periods of from two to thirty days. Before administration of the dye he had an average of 30 petit mal seizures a day, and there was no day without spells. Petit mal attacks have been less severe since administration of the dye, and grand mal attacks, which have always been rare, are now of the same or greater severity.

The patient before treatment exhibited purposeless activity, but during and after administration of dye he became quieter, coincident with diminution and temporary cessation of seizures.

CASE 3.—J. C., a white boy aged 15, with left hemiplegia and a mental age of 3½ years, whose seizures began at 6 months of age, had been at the Monson State Hospital for the past eight years. The family history was irrelevant. Birth was with instruments, and the head was considerably deformed. There was no paralysis at the time of birth. When the patient was between 8 and 9 years of age, paralysis of the left side was noted; this became more pronounced and was marked at the time of the study. The left side of the body was smaller than

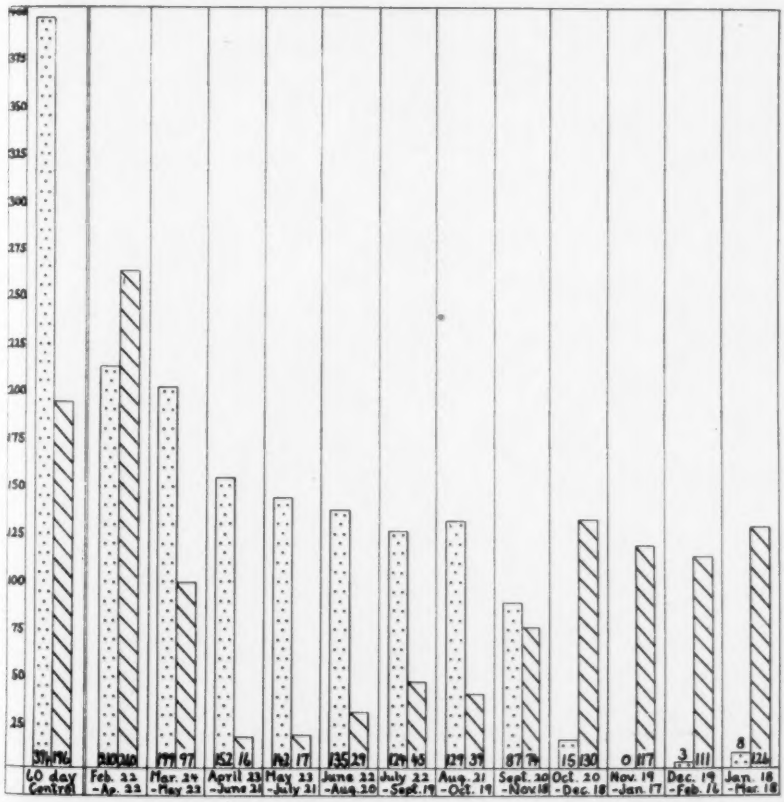

Chart 1 (case 1).—Anticonvulsant effects of treatment with brilliant vital red on a boy aged 16, weighing 97 pounds (44 Kg.), who had had idiopathic epilepsy for ten and a half years. A total of 2,214 cc. of a 1 per cent solution of the dye was given.

In this chart and the accompanying charts, the columns with dots indicate petit mal seizures, and those with lines, grand mal seizures.

the right. Talking, walking and teething were delayed. The patient had had no significant illnesses or injuries in childhood.

Epilepsy began at the age of 6 months. The seizures started on the hemiplegic side. Most of the convulsions were of the grand mal type.

Physical Examination.—There were: facial asymmetry; a congenital hemangioma involving the right side of the nose, the right half of the forehead, the right half

of both lips and a small area on the right side of the chin; spastic left hemiplegia; paralysis of the left side of the face; underdevelopment of the left extremities, which were smaller than the right, and hyperactive reflexes on the left side.

Diagnosis.—The diagnosis was epilepsy, symptomatic of hemangioma.

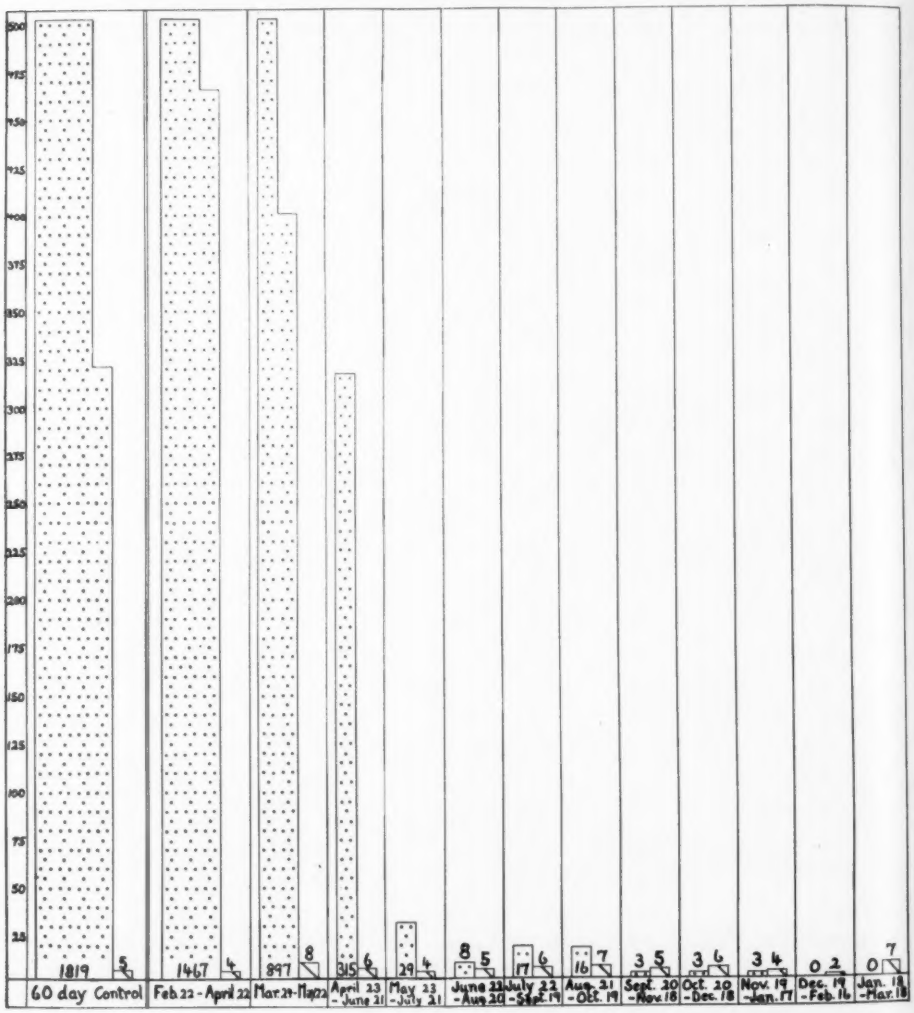

Chart 2 (case 2).—Anticonvulsant effects of treatment with brilliant vital red on a boy aged 11 years, weighing 66 pounds (29.9 Kg.), who had had symptomatic epilepsy for seven years. A total of 1,456 cc. of a 1 per cent solution of the dye was given.

Medication.—Phenobarbital, 1½ grains (0.097 Gm.), was administered morning and night before and during the study.

Brilliant Vital Red: Administration was begun on February 22, interrupted on April 26, resumed on May 14 and terminated on July 12, 1937. The patient received a total of 2,434 cc. of a 1 per cent solution of the dye.

Effect on Convulsions.—In the sixty day period of observation before administration of the dye, the patient had 16 petit mal and 58 grand mal seizures. Between April 23 and June 21, the sixty day period when seizures were least numerous, he had 5 petit mal and 9 grand mal seizures. Since, convulsions gradually increased in number, and during the last five months prior to the time of writing they were nearly as frequent as before dye therapy was begun. Grand mal convulsions were less severe throughout the period of study. Petit mal convulsions were less severe during the first nine months of observation.

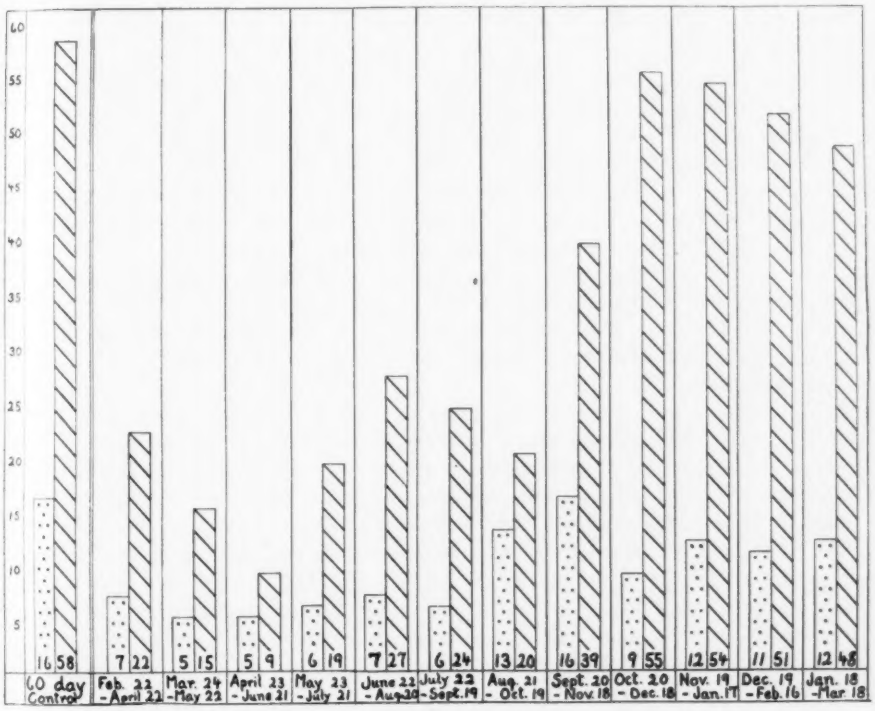

Chart 3 (case 3).—Anticonvulsant effects of treatment with brilliant vital red on a boy aged 15 years, weighing 80 pounds (36.3 Kg.), who had had symptomatic epilepsy for fourteen and a half years. A total of 2,434 cc. of a 1 per cent solution of the dye was given.

From about the second to the fifth week of administration of the dye the patient was more talkative, active, alert and noisy. After that, he reverted to his previous state.

Renal "irritation" was slight.

Case 4.—R. C., a well developed and well nourished white boy aged 9, with a mental age of 7 years and 10 months, had had seizures since the age of 7 years and had been at the Monson State Hospital for one and a half years. The family history revealed that a paternal uncle "was said to have had some sort of attacks" and had committed suicide. The past history of the patient was without significance except for the onset of epilepsy.

Physical Examination.—The results were essentially normal. The patient was restless, excitable and inattentive.

Ventriculoencephalograms made in 1934 showed that the left ventricle was slightly smaller than the right but revealed no other abnormality.

Diagnosis.—The diagnosis was idiopathic epilepsy with mental deficiency.

Medication.—Phenobarbital, 1 grain (0.065 Gm.), was administered morning and night before and during the study, except from March 6 to April 2, when the dose was doubled because of sudden temporary increase in frequency of seizures during the early part of administration of the dye.

Brilliant Vital Red: Administration was begun on February 22 and was terminated on April 25, 1937; a total of 1,470 cc. of a 1 per cent solution was given.

Effect on Convulsions.—In the sixty day period of observation before administration of the dye the patient had 73 petit mal and 38 grand mal seizures. Convulsions increased greatly in number during the period of injection and did not return to the original level until several weeks after administration was terminated. In the sixty day period between March 24 and May 22, at the height of treatment, the patient had 340 petit mal and 39 grand mal attacks. After this initial rise in the frequency of seizures, there was a temporary fall below the level of the period of control. Since then the number of convulsions has been about the same or less. The patient left the hospital on Dec. 1, 1937. In the sixty day observation period from June 22 to August 20 he had 19 petit mal and 13 grand mal spells, which was less than during any other sixty day period. Both types of seizure were less severe.

A combination of three considerations decided us to forego further injections of dye: (1) considerable renal "irritation," which, however, disappeared later; (2) marked increase in the number of spells, and (3) more rapid deterioration since administration of the dye. Evidence of renal "irritation" subsided in five weeks. In June the patient had returned to his previous condition in all respects.

Excessive flow of tears and salivation occurred during the period of administration of dye, and, according to the attendant, "half the time the patient could not feed or help himself in any way." The character of the spells remained the same, but they were more numerous. The changes in general behavior were those associated with mental deterioration. Six weeks after administration of dye was stopped the patient gradually approached the former mental status.

Case 5.—J. W. M., a well developed and well nourished white boy aged 15, with a mental age of 5 years and 4 months, whose seizures began at the age of 4 days, had been at the Monson State Hospital for four years. The family history was irrelevant. The patient was born by difficult labor, high forceps causing a small scar on the forehead. The early development was not remarkable except for the convulsions. At the age of 4½ years congenital cataracts were discovered, and operations were performed. The patient's first convulsion, at the age of 4 days, was severe. He was jaundiced at the time. Subsequent seizures occurred nearly every day, and at 6 months of age they were more severe. At present convulsions are of both the petit mal and the grand mal type.

Physical Examination.—On admission in 1932 there were inconstant, horizontal nystagmus; irregularity in shape of the pupils, and weakness of the musculature of the right side of the face. In 1933 the gait was clumsy; the attitude of the body was rigid, and the posture of the head, trunk and extremities

was fixed; passive movements revealed resistance; the tendon reflexes were exaggerated; the left plantar response was flexor; Barre's sign was present on the right. In 1936 the right knee jerk was hyperactive.

Diagnosis.—The diagnosis was symptomatic epilepsy (due to birth injury) with mental deficiency.

Medication.—Phenobarbital, ¾ grain (0.048 Gm.), was administered morning and night before and during the study.

Brilliant Vital Red: Administration was begun on February 22, interrupted on April 25, resumed on May 14 and terminated on July 12, 1937. A total of 2,142 cc. of a 1 per cent solution of the dye was given.

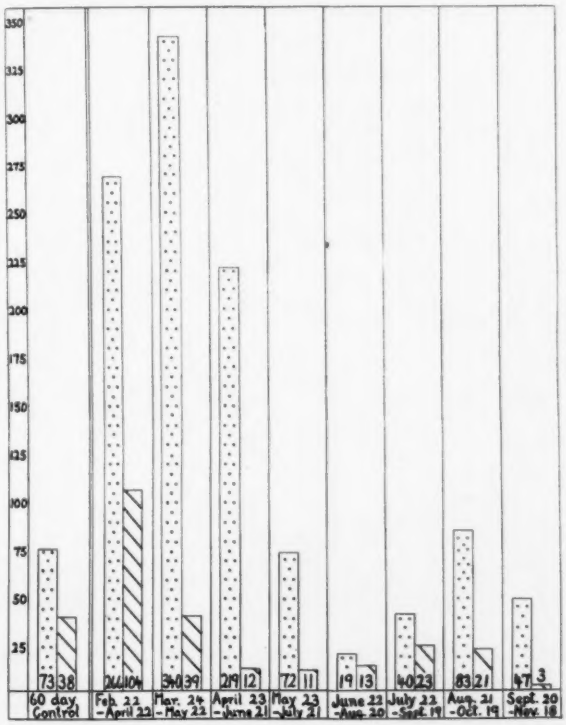

Chart 4 (case 4).—Anticonvulsant effects of treatment with brilliant vital red on a boy aged 9 years, weighing 74 pounds (33.6 Kg.), who had had idiopathic epilepsy for two years. A total of 1,470 cc. of a 1 per cent solution of the dye was given.

Effect on Convulsions.—While the number of grand mal attacks did not change appreciably during or after dye therapy, there was a slight, gradual reduction in the number of petit mal attacks. Petit mal spells were of the same severity as before; grand mal seizures were less severe. The patient left the hospital in November 1937.

The general behavior of the patient showed definite change. Whereas before treatment he was inactive, "dopey" and usually obedient, several weeks after treatment he became very active, excitable, disagreeable, quarrelsome, noisy and

disobedient. In a few weeks he became quieter, but he is still more alert and takes a more active interest in his environment than formerly. The character of his spells did not change.

Renal "irritation" was slight.

CASE 6.—R. S., a well developed and well nourished white boy aged 14, with a mental age of 4 years and 8 months, had the first epileptic attack at the age of 6 months and had been at the Monson State Hospital for four years. The maternal grandfather was a heavy drinker; the maternal grandmother had "fainting spells"; one maternal aunt had 32 convulsions in twenty-four hours while teething and died; another maternal aunt was committed to a state hospital for mental diseases for six weeks after parturition; a third maternal aunt had a "fainting spell" at the age of 14 years; a maternal uncle had convulsions and sick headaches; the father was alcoholic; the mother had severe sick headaches, and a sister had "fainting spells."

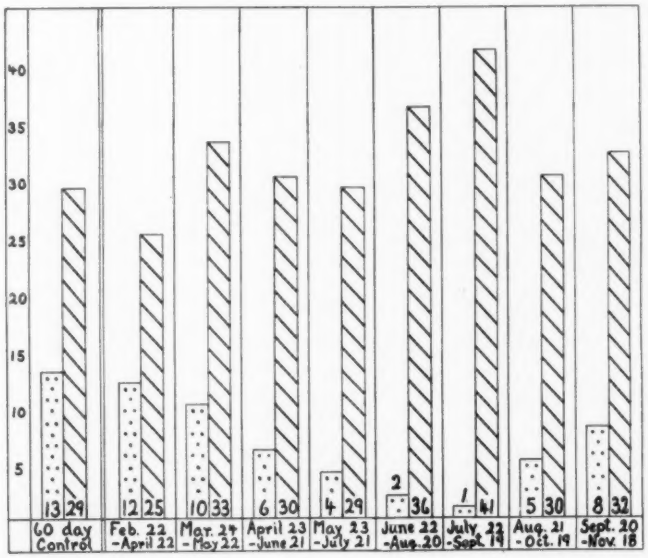

Chart 5 (case 5).—Anticonvulsant effects of treatment with brilliant vital red on a boy aged 15 years, weighing 103 pounds (46.7 Kg.), who had had symptomatic epilepsy for fifteen years. A total of 2,142 cc. of a 1 per cent solution of the dye was given.

The past history of the patient was not remarkable except for convulsions. The first seizure was at the age of 6 months, and the second, at 8 years, when he was unconscious for seven hours; subsequent attacks occurred every few weeks or months until the past few years, when he had an average of 20 a month. Nearly all the seizures were of the grand mal type.

Physical Examination.—The patellar and achilles reflexes were more active on the left side than on the right.

Diagnosis.—The diagnosis was idiopathic epilepsy (hereditary) with mental deterioration.

Medication.—Phenobarbital, 1½ grains (0.097 Gm.), was administered morning and night before and during the study.

Brilliant Vital Red: Administration was begun on February 22, interrupted on April 25, resumed on May 14 and terminated on May 18, 1937. The patient received a total of 1,269 cc. of a 1 per cent solution of the dye.

Effect on Convulsions.—The number and severity of the convulsions remained essentially unchanged.

Course.—Renal "irritation" was a troublesome factor in this case. Red blood cells appeared frequently in the urine, often in large numbers. Degenerated, granular cells and finely granular casts were numerous by the eighth week.

The patient complained twice of pain in the epigastrium for several hours; it came on shortly after injection of the dye.

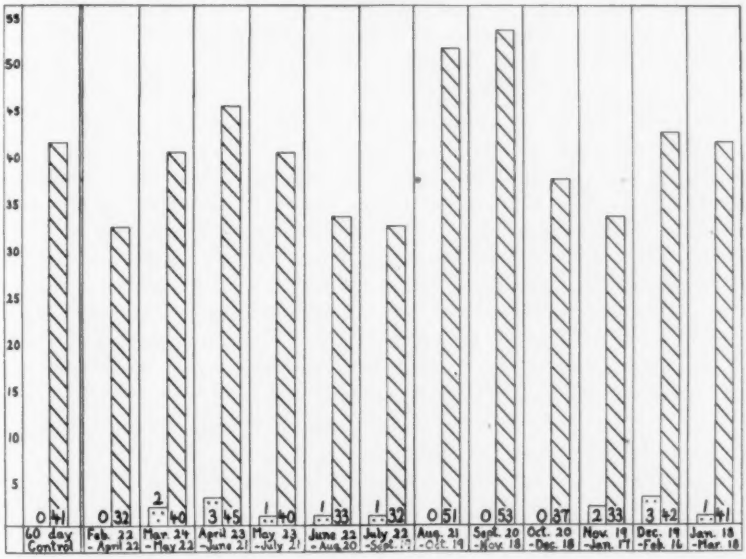

Chart 6 (case 6).—Anticonvulsant effects of treatment with brilliant vital red on a boy aged 14 years, weighing 109 pounds (49.4 Kg.), who had had idiopathic epilepsy for thirteen and a half years. A total of 1,269 cc. of a 1 per cent solution of the dye was given.

The patient was slightly more active and alert for a short time early in the treatment.

Case 7.—F. R., a well developed and well nourished white boy aged 15, 5 feet and 7 inches (170 cm.) in height, with a mental age of 5½ years, whose first attack occurred at the age of 3 days, had been at the Monson State Hospital for seven years. The family history was irrelevant.

At 3 days of age the patient suddenly became unconscious; he did not convulse or shake, but cried at that time. Birth was not abnormal. According to the mother, the child gained slowly and was thin and "backward in everything." At the age of 1 year he had a severe epileptic seizure, beginning with a cry, was unconscious and convulsed. He had both petit mal and grand mal convulsions.

Physical Examination.—There were bilateral strabismus and unsteadiness in gait.

Diagnosis.—The diagnosis was symptomatic epilepsy with mental deficiency.

Medication.—Phenobarbital, 1½ grains (0.097 Gm.), was administered morning and night before and during the study.

Brilliant Vital Red: Administration was begun on March 3, interrupted on April 26, resumed on May 14 and terminated on May 18, 1937. A total of 1,412 cc. of a 1 per cent solution of the dye was given.

Effect on Convulsions.—The petit mal attacks doubled in number in the two months during which the patient was receiving dye, then gradually decreased and approached the original level after the injections were terminated. The grand mal attacks showed little change. Petit mal spells were of the same severity; grand mal seizures were less severe.

Course.—Renal "irritation" was slight.

In general, the behavior of the patient showed no appreciable change.

The patient died on July 13, during convulsions. He had been in apparent good health up to the time of death.

Autopsy.—There were: pulmonary congestion and edema; cerebral edema; internal hydrocephalus; a "primary complex" of active pulmonary tuberculosis, of recent origin; staining of all the viscera with brilliant vital red, and enlargement of the liver and spleen. Frozen sections of the liver showed all the Kupffer cells to be heavily laden with granules of brilliant vital red. Phagocytes of the spleen and lymph nodes also showed much intracellular pigment. Sections of the kidneys showed rare, minute particles of dye in the cells of the glomeruli; there was no scarring; some of the convoluted tubules showed slight fatty degeneration of the epithelial cells. No dye was seen in the cells of the spinal cord or brain. The cisternal and lumbar spinal fluid was clear and colorless at autopsy, and the protein content and cytologic reaction were normal.

Case 8.—E. O. S., an underdeveloped white boy aged 11, with a mental age of 4 years and 8 months, had the first seizure at the age of 6 years and had been at the Monson State Hospital for three years. The family history showed that a maternal uncle and aunt and the patient's mother had epilepsy. The patient had been well up to the time of onset of convulsions. Seizures occurred two or three times a week on the average. A ketogenic died was tried in 1931, with no lasting beneficial effect. In 1932 the patient's behavior changed markedly: "He wanted to be climbing all the time, didn't seem to know what he was doing and soiled his clothes during the daytime." He had more grand mal than petit mal seizures.

Physical Examination.—In 1933 the findings were not remarkable. In 1934 the righ knee jerk was hyperactive and pendulous. In 1935 both knee jerks were hyperactive.

Diagnosis.—The diagnosis was idiopathic epilepsy with mental deficiency.

Medication.—Phenobarbital, ¾ grain (0.048 Gm.), was administered morning and night before and during the study.

Brilliant Vital Red: Administration was begun on March 1 and was terminated on April 25, 1937. The patient received a total of 1,124 cc. of a 1 per cent solution of the dye.

Effect on Convulsions.—The average number of both petit and grand mal seizures after dye therapy was more than twice that in the sixty day period serving as a control. Both types of spells were less severe.

Course.—There was evidence of considerable renal "irritation."

The general behavior of the patient changed markedly for a few weeks, until administration of dye was stopped. Whereas before treatment he was excitable, active, troublesome and quarrelsome, during the treatment he lost all energy,

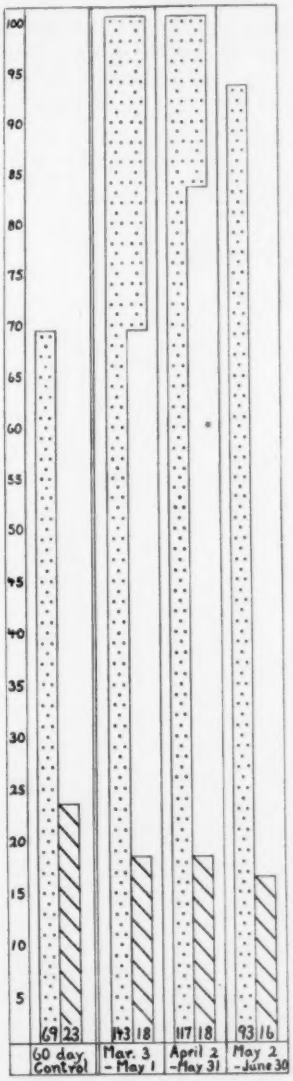

Chart 7 (case 7).—Anticonvulsant effects of treatment with brilliant vital red on a boy aged 15 years, weighing 114 pounds (51.7 Kg.), who had had symptomatic epilepsy for fifteen years. A total of 1,412 cc. of a 1 per cent solution of the dye was given.

became drowsy and apathetic and was at times in semistupor. Tears and saliva flowed in large amounts during the period of administration of the dye.

CASE 9.—G. P., a well developed and well nourished white boy aged 12, large for his age, with a mental age of 5 years and 2 months, had had seizures since the age of 3 years and had been at the Monson State Hospital for three years. The family history was irrelevant. The patient was born two months prematurely; the weight at birth was 5 pounds (2,267 Gm.). He was a "fretful baby and cried day and night." He had a severe attack of pertussis at the age of 2 months. He was slow in talking, began to walk at the age of 16 months and was unsteady on his feet; "one leg did not move right." The first convulsion was mild; later seizures were severe. Use of phenobarbital checked convulsions

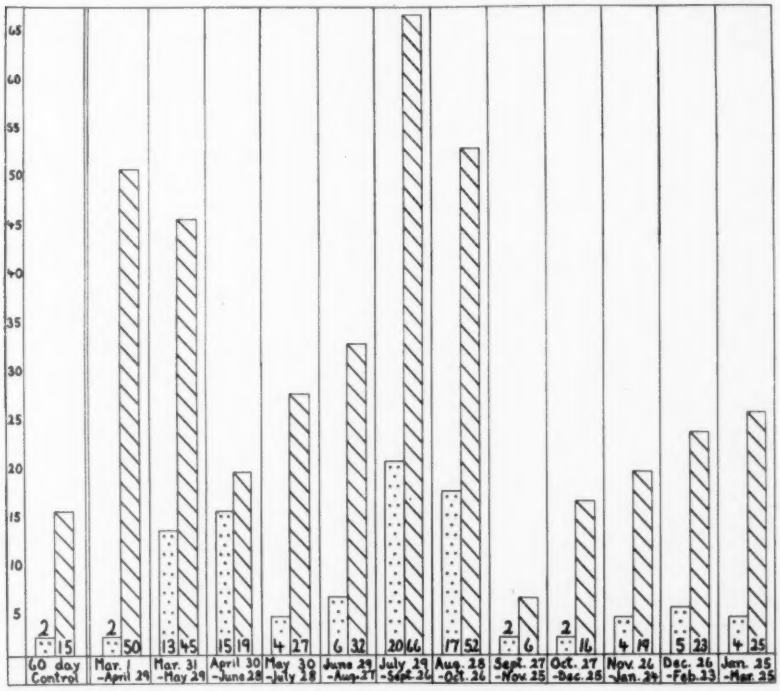

Chart 8 (case 8).—Anticonvulsant effects of treatment with brilliant vital red on a boy aged 11 years, weighing 68 pounds (30.8 Kg.), who had had idiopathic epilepsy for five years. A total of 1,124 cc. of a 1 per cent solution of the dye was given.

for months at a time; when the drug was omitted many severe convulsions recurred.

Physical Examination.—The results were normal.

Diagnosis.—The diagnosis was idiopathic epilepsy and mental deficiency.

Medication.—Phenobarbital, 1½ grains (0.097 Gm.), was given morning and night before and during the study.

Brilliant Vital Red: Administration was begun on March 3, interrupted on April 26, resumed on May 28 and terminated on July 8, 1937. The patient received a total of 2,509 cc. of a 1 per cent solution of the dye.

Effect on Convulsions.—In the sixty day period of observation before administration of the dye the patient had 97 petit mal and 74 grand mal seizures. After administration of the dye was begun, both the petit and the grand mal seizures were markedly diminished in number. In the sixty day period between April 2 and May 31 the patient had 27 petit mal and 10 grand mal seizures, the smallest

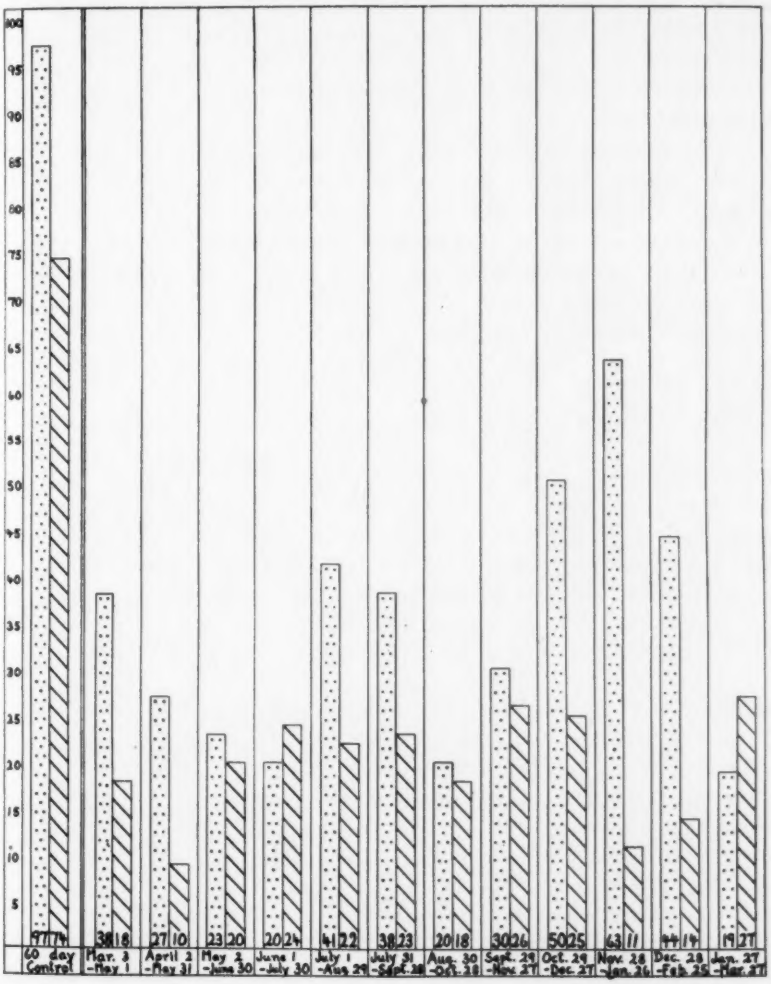

Chart 9 (case 9).—Anticonvulsant effects of treatment with brilliant vital red on a boy aged 12 years, weighing 103 pounds (46.7 Kg.), who had had idiopathic epilepsy for seven years. A total of 2,509 cc. of a 1 per cent solution of the dye was given.

number in the whole period of observation. Both types of convulsions are now less severe.

Course.—There was little evidence of renal "irritation."

The behavior changed considerably during the first two months of treatment. Before injections of the dye the patient was quiet and "never had a word to say

to any one." During treatment he was alert and active, and frequently quarrelsome. There was also increased salivation. Since May, he had become quieter, but was still more active than before administration of the dye.

CASE 10.—H. M., an underdeveloped and malnourished white boy aged 9 years, with a mental age of 3 years and 2 months, began to have convulsions at the age of 2½ years and had been at the Monson State Hospital for five years. The family history was irrelevant. The patient had influenza in January 1929; the first convulsion occurred in June 1929; in 1931, at 5 years of age, there were progressive loss of speech and sudden loss of strength in the legs, resulting in a staggering gait.

Physical Examination.—There were: poor development; a rachitic rosary and Harrison's groove; hyperactive abdominal reflexes and knee jerks; unsteadiness of gait, with the trunk bent forward, and genu varum.

Diagnosis.—The diagnosis was idiopathic epilepsy with mental deficiency.

Medication.—Phenobarbital, ¾ grain (0.048 Gm.), was given morning and night before and during study.

Brilliant Vital Red: Administration was begun on March 1 and was continued until April 25, 1937. A total of 1,392 cc. of a 1 per cent solution of the dye was given.

Effect on Convulsions.—It is difficult to interpret the effect of the dye on the convulsions over the period of a year. We think that the dye was responsible for the increased number of seizures in the first four or five months. Whether the dye influenced the seizures in the last seven or eight months is questionable, since the patient had for years been subject to periods characterized by a large number of seizures alternating with periods when seizures were relatively few. On the whole, we think that the dye was of no benefit and may have precipitated more convulsions. Petit mal spells were of the same severity up to January 1938, and grand mal attacks were less severe up to February 1938. Both have been more severe since.

Course.—There was marked renal "irritation."

Drowsiness and an increased desire to sleep were the only noteworthy changes in the early part of treatment; they were transient.

CASE 11.—R. A. L., a well developed and well nourished white boy aged 12 years, 5 feet and 5 inches (165.1 cm.) in height, with a mental age of 5 years and 8 months, had had seizures since 2 years of age and had been at the Monson State Hospital four years. The family history was irrelevant. The patient was born one month prematurely, his weight at birth being 6 pounds (2,721 Gm.); poor eyesight was noted at the age of 5½ years, and nystagmus was also observed at an early age. Between 2 and 5 years of age the patient had 3 or 4 spells, then none until he was 8 years of age. Since, he had had an attack every ten days on the average. In 1932, at the age of 7 years, a diagnosis of hypermature cataract of the left eye and glaucoma of the right eye was made; operations were performed.

Physical Examination.—The significant findings were facial asymmetry, atrophy of the optic nerve and a gait with a wide base.

Diagnosis.—The diagnosis was idiopathic epilepsy with mental deficiency.

Medication.—Phenobarbital, ¾ grain (0.048 Gm.), was given morning and night before and during the study.

Brilliant Vital Red: Administration was begun on March 3, interrupted on April 26, resumed on May 14 and terminated on May 24, 1937. The patient received a total of 1,794 cc. of a 1 per cent solution of the dye.

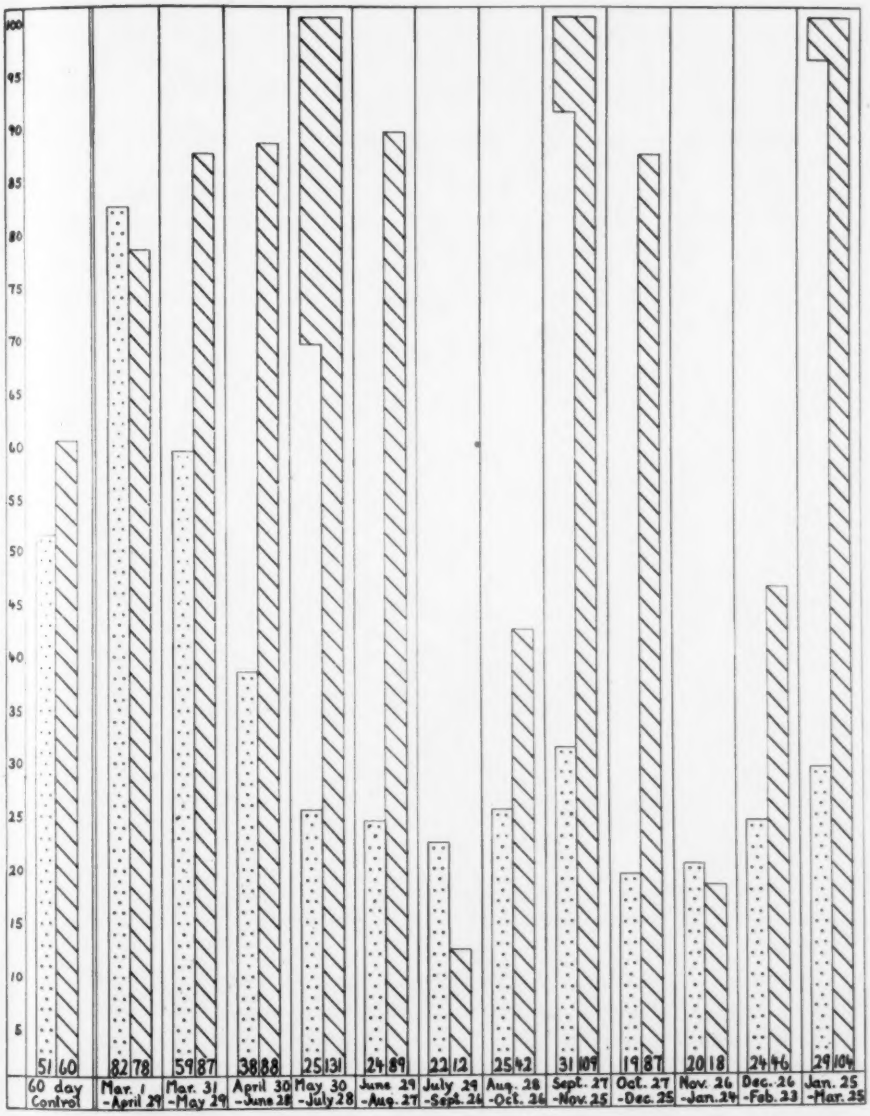

Chart 10 (case 10).—Anticonvulsant effects of treatment with brilliant vital red on a boy aged 9 years, weighing 62 pounds (28.1 Kg.), who had had idiopathic epilepsy for six and a half years. A total of 1,392 cc. of a 1 per cent solution of the dye was given.

Effect on Convulsions.—The effect was similar to that in case 4; the seizures increased in number during and shortly after administration of the dye and then

returned to about the original level. On the whole, we believe that the dye had an unfavorable effect on the number of spells. Both petit and grand mal seizures were less severe.

Course.—The patient was more alert, active and quarrelsome for a few weeks early in the course of treatment.

There was moderate renal "irritation."

CASE 12.—R. S. F., an underdeveloped and well nourished white boy aged 8, with a mental age of 5 years, had had convulsions since the age of 3 years and had been at the Monson State Hospital for one and a half years. The family history was irrelevant. The patient's past history was not remarkable, except for convulsions. At the onset of the seizures the patient had both petit mal and grand mal attacks. For the past two years or more most of the convulsions had been of the grand mal type.

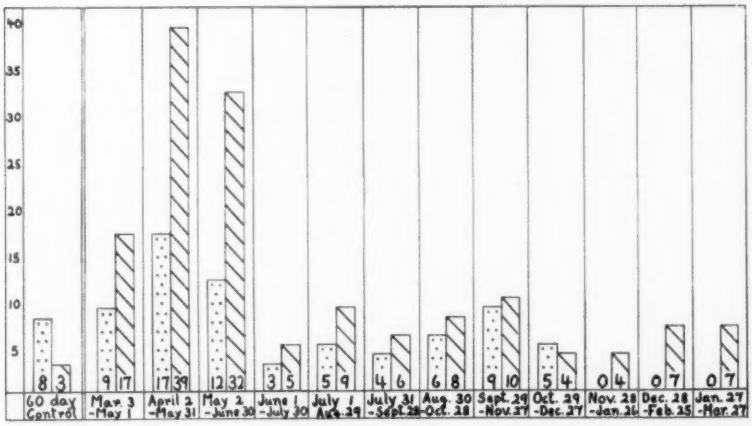

Chart 11 (case 11).—Anticonvulsant effects of treatment with brilliant vital red on a boy aged 12 years, weighing 107 pounds (48.5 Kg.), who had had idiopathic epilepsy for ten years. A total of 1,794 cc. of a 1 per cent solution of the dye was given.

Physical Examination.—The patient had a tendency to keep the tongue directed against the right cheek and to protrude it to the right; both knee jerks were hyperactive.

Diagnosis.—The diagnosis was idiopathic epilepsy and mental deficiency.

Medication.—Phenobarbital, ½ grain (0.032 Gm.), was given morning and night before and during the study.

Brilliant Vital Red: Administration was begun on March 3 and interrupted on March 5, on account of sore throat and fever; it was resumed on March 16, interrupted on April 25, resumed on May 15 and terminated on July 12, 1937. The patient received a total of 1,773 cc. of a 1 per cent solution of dye.

Effect on Convulsions.—In the sixty day period of observation before administration of dye the patient had no petit mal and 26 grand mal seizures. In the sixty day period between June 1 and July 30 he had no petit mal and 15 grand mal seizures. There was a slight decline in the number of spells during the first nine months. Since, seizures were about as frequent as before dye therapy

was begun. The severity of the grand mal convulsions was less, and petit mal attacks appeared for the first time.

Course.—The patient was drowsy for the first three or four weeks of treatment; after that he reverted to his original state.

Evidence of renal "irritation" was slight. The patient vomited several times a few hours after from 40 to 50 cc. of a 1 per cent solution of the dye was given; on two occasions, once early in the treatment and once later, the rectal temperature was 103.8 F. for several hours after injection of the dye.

Case 13.—H. P. B., an underdeveloped white boy aged 11, with a mental age of 5 years, had convulsions since the age of 3½ years and had been at the Monson State Hospital for four years. The family history was irrelevant. Up to the onset of epilepsy the history of the patient was not remarkable, except that he did not talk until the age of 2 years. The first convulsion was of the grand mal type; subsequent seizures for the following two years were all of the same type and occurred about once a month. Then petit mal seizures also appeared.

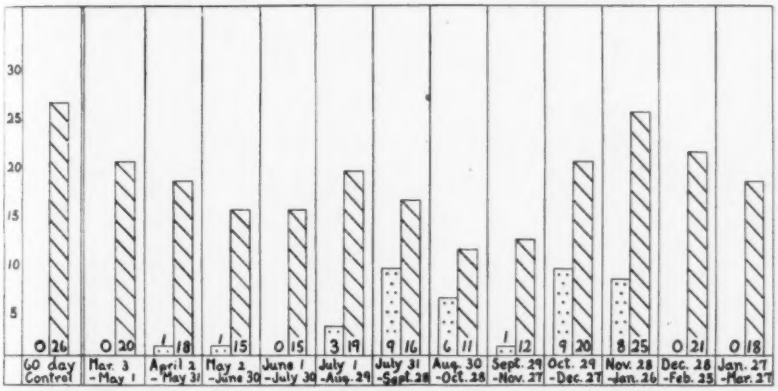

Chart 12 (case 12).—Anticonvulsant effects of treatment with brilliant vital red on a boy aged 8 years, weighing 61 pounds (27.7 Kg.), who had had idiopathic epilepsy for five years. A total of 1,773 cc. of a 1 per cent solution of the dye was given.

Physical Examination.—In 1932 the results were negative. In 1936 the knee jerks were hyperactive.

Diagnosis.—The diagnosis was idiopathic epilepsy with mental deficiency.

Medication.—Phenobarbital, ¼ grain (0.048 Gm.), was given morning and night before and during the study.

Brilliant Vital Red: Administration was begun on March 3 and was terminated on April 19, 1937, because convulsions were steadily increasing in number. The patient received a total of 1,194 cc. of a 1 per cent solution of the dye.

Effect on Convulsions.—At the beginning of the administration of dye the number of grand mal seizures increased for a few weeks and then returned to, or fell below, the previous level. Petit mal seizures steadily decreased in number, and five months after the beginning of administration of the dye they ceased for a month and then returned, but never to the level of the sixty day period of

Summary of Significant Data and Results of Injection of Brilliant Vital Red on Patients with Epilepsy

Case	Age, Yr.	Diagnosis	Duration of Epilepsy, Yr.	Weight Before and After Injection of Brilliant Vital Red. Lb.		Amount of Brilliant Vital Red, Cc. of 1% Solution	Frequency of Petit Mal Attacks	Severity of Petit Mal Attacks	Frequency of Grand Mal Attacks	Severity of Grand Mal Attacks	Change in Disposition	Duration of Change in Disposition
				Before (Feb.)	After (July)							
1	16	Idiopathic epilepsy	10½	97	105	2,214	Less	Less severe at height of treatment only	Less	Less severe at height of treatment only	None	No change
2	11	Symptomatic epilepsy	7	66	69	1,456	Less	Less	Same	More or same	More purposeful activity; "brighter"	To date
3	15	Symptomatic epilepsy	14½	80	80	2,434	Less	Less severe for first 9 months	Less	Less	More alert, active and talkative	From second to fifth week
4	9	Idiopathic epilepsy	2	74	83	1,470	More at height of dye treatment	Less	More at height of dye treatment	Less	Drowsy and apathetic	During period of dye administration
5	15	Symptomatic epilepsy	15	103	102	2,142	Less	Same	Same	Less	More active; excitable; quarrelsome	To date, but changes are less marked during last 6 mo.
6	14	Idiopathic epilepsy	13½	109	110	1,269	Six during dye treatment only	.....	Same	Same	More active and alert	Few weeks early in treatment
7	15	Symptomatic epilepsy	15	114	117	1,412	More	Same	Slightly less	Less	None	No change
8	11	Idiopathic epilepsy	5	68	66	1,124	More	Less	More	Less	Drowsy and apathetic	During period of dye administration
9	12	Idiopathic epilepsy	7	103	103	2,509	Less	Less	Less	Less	Very alert, active and quarrelsome	To date, but less so since May
10	9	Idiopathic epilepsy	6½	62	60	1,392	More during dye treatment; less after	Same severity to Jan. 1938; more severe since	More during and after dye treatment	Less severe up to Feb. 1938; more severe since	Drowsy early; transient	First few weeks
11	12	Idiopathic epilepsy	10	107	110	1,794	More during dye treatment; same later	Less	More at height of dye treatment	Less	More alert and active; quarrelsome	Few weeks only in period of dye administration
12	8	Idiopathic epilepsy	5	61	59	1,773	Two during dye treatment only	.....	Slightly less	Less	Drowsy	First 3-4 weeks of period of dye administration
13	11	Idiopathic epilepsy	7½	67	69	1,194	Less	Less	Same	Same	Disturbed; "brighter"; bladder control	Duration period of dye administration

control. In the last two sixty day periods, the number of grand mal seizures increased while that of the petit mal seizures diminished. Petit mal seizures were less severe, and the severity of the grand mal seizures remained unchanged.

Course.—Renal "irritation" was slight.

During the first week of treatment the patient was disturbed and then became "brighter" for a few weeks; after the injections of dye were stopped he returned to his original state. During most of the period of administration of dye he had control of the bladder, but after termination of treatment he wet himself as he always had.

RESULTS

The effect of brilliant vital red on the number of spells in our series of cases is shown graphically in the individual charts and is indicated briefly in the table, which summarizes the significant observations. Since considerable spontaneous variation in the frequency of seizures

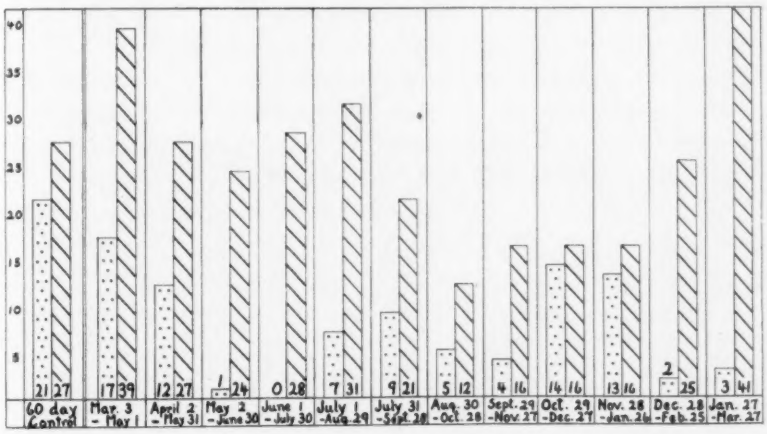

Chart 13 (case 13).—Anticonvulsant effects of treatment with brilliant vital red on a boy aged 11 years, weighing 67 pounds (30.4 Kg.), who had had idiopathic epilepsy for seven and a half years. A total of 1,194 cc. of a 1 per cent solution of the dye was given.

from month to month and year to year is common in patients with epilepsy, only marked changes in the frequency of seizures following administration of brilliant vital red can be regarded as significant.

1. Both petit and grand mal seizures were significantly reduced in number in 3 patients (cases 1, 3 and 9).

2. The number of petit mal seizures only was markedly reduced in 3 patients (cases 2, 5 and 13), while that of the grand mal seizures remained about the same.

3. Grand mal seizures were significantly reduced in number in 1 patient (case 12). This patient had never been known to have petit mal seizures until brilliant vital red was administered.

4. Petit and grand mal seizures were considerably increased in number in 4 patients (cases 4, 8, 10 and 11). This we attribute directly to the dye, since the increased frequency of seizures persisted throughout the period of administration of dye and for weeks or months thereafter.

5. Petit mal seizures were greatly increased, while grand mal seizures remained about the same in 1 patient (case 7). This we also attribute to the direct action of the dye.

6. No significant change occurred in 1 patient (case 6).

Of all the patients in our series, the boy in case 2 showed the most outstanding improvement. Before injections of dye were begun he averaged about 30 petit mal seizures a day and had 2 or 3 grand mal attacks in a month. Shortly after he had received 1,456 cc. of dye the petit mal seizures decreased in frequency to the point at which he was free from attacks for from several days to three weeks. The number of grand mal attacks, however, was not affected by the dye. The petit mal seizures were less severe since the beginning of dye therapy. The grand mal convulsions, on the other hand, were just as, and sometimes more, severe coincident with and following the administration of dye.

Examination of the charts shows that the anticonvulsant effect of brilliant vital red, whether favorable or unfavorable, began to appear, as a rule, within the first few weeks of treatment and continued for several months and that thereafter these effects diminished the longer the interval after treatment. Toward the end of the period of study, the frequency of convulsions approached the level before the administration of dye. Case 2 is the most marked exception. In this case, it will be noted, seizures progressively diminished for over a year.

The anticonvulsant effect of brilliant vital red on both petit mal and grand mal attacks in 13 patients during a period of from five to thirteen months may be briefly summarized, as follows: 1. Seven patients (cases 1, 2, 3, 5, 9, 12 and 13), or 53.8 per cent, had fewer seizures. 2. Five patients (cases 4, 7, 8, 10 and 11), or 38.5 per cent, had more seizures. 3. One patient (case 6), or 7.6 per cent, was unaffected.

In most cases the seizures were less severe during and after the period of administration of dye (see table).

Changes in disposition associated with dye treatment were noted in 11 of the 13 patients (see table). Seven of the 11 patients were "brighter," more active or quarrelsome; the other 4 were drowsy or apathetic. These changes appeared usually within the first week or two of the period of injection of dye. In 4 of the 7 patients who were "brighter," the changes lasted only from two to four weeks; in the

other 3 patients the changes have continued to date, though to a lesser degree since cessation of the injections. The 4 patients who became drowsy returned to their former state soon after administration of dye was stopped.

In this small series of cases it is impossible to make any significant correlation between the effect of brilliant vital red on spells and such factors as age, weight, duration of illness, diagnosis ("idiopathic" or "symptomatic") and amount of dye given. Therefore, one cannot at present select patients with any assurance that they will benefit from treatment with brilliant vital red. Each case is an experiment in itself. In the course of this study, however, we were impressed by an observation which may be helpful in predicting early in the course of treatment the effects to be expected; we do not intend to make this an inflexible rule, since exceptions may occur in which no rules can be applied. In most instances, if brilliant vital red is to prove beneficial, the number of spells will begin to decrease early, or will decrease after a short preliminary increase in frequency. If, after a few weeks of administration of dye the number of seizures remains about the same or continues to rise, further injections of brilliant vital red will probably be of no avail in reducing the frequency of spells.

A second observation concerns the amount of dye that it is desirable to give. Such large amounts of dye as we gave to most of our patients are probably not necessary to produce the maximal favorable effect on the frequency of seizures. We believe that dye in excess of from 1,200 to 2,000 cc. of a 1 per cent solution, depending on the weight of the patient, does little or no good. However, if the number of spells continually decreases when these limits have been reached, further administration of dye is justifiable. All but 1 of the patients treated by Cobb, Cohen and Ney [3] received considerably less brilliant vital red than did ours; yet their results were similar to ours. Except for 2 patients who received 1,396 and 1,043 cc., respectively, of a 1 per cent solution of dye, their patients received from 115 to 889 cc. of the 1 per cent solution of dye. The amount of dye we gave ranged from 1,194 to 2,509 cc. of a 1 per cent solution. Our experience, based on the present series of patients, together with 4 others treated more recently, has taught us that the safest and most satisfactory procedure in the administration of brilliant vital red is as follows: At the beginning, from 10 to 15 cc. of a 1 per cent solution of the dye is given each day for two or three days; dye is omitted for a day after these small initial doses; then 30 cc. of a 1 per cent solution is given two or three days in succession, followed by omission on one day. This procedure, in our experience, has been accompanied by the least amount of renal irritation and other untoward effects.

SUMMARY

1. The rationale of brilliant vital red as a clinical anticonvulsant is explained briefly.

2. The mode of absorption and excretion of brilliant vital red is described.

3. The effects of brilliant vital red on convulsions and behavior in 13 cases of epilepsy during from a four to a twelve month period are described and tabulated; 10 of 13 cases were observed for twelve months.

4. Transitory untoward effects and renal irritation associated with brilliant vital red therapy are discussed.

CONCLUSIONS

1. Brilliant vital red diminished the number and severity of epileptic seizures in a little over one half of the cases.

2. Brilliant vital red was of no benefit in a little less than one half of the cases; in fact, in several cases its use was associated with an increased number of seizures; in the majority of these cases, however, the severity of the seizures was diminished.

3. Brilliant vital red tended to have a greater anticonvulsant effect on petit mal than on grand mal seizures.

4. Brilliant vital red in large amounts caused temporary renal "irritation," but no signs or symptoms of permanent renal damage.

NOTE.—Since this article was submitted for publication, studies by Aird [6] on the permeability of the endothelium in dogs have shown that intravenous injection of brilliant vital red definitely reduces the amount of cocaine hydrochloride entering the cerebrospinal fluid. Aird concluded that the effect of the dye was attained by alteration in the permeability of the "endothelial barrier" to "convulsive metabolites."

6. Aird, R. B.: Studies on Tissue Permeability as a Factor in Epilepsy: The Mode of Action of Brilliant Vital Red in Epilepsy, read at the meeting of the American Psychiatric Association, San Francisco, June 6, 1938.

OXYCEPHALY

A NEW OPERATION AND ITS RESULTS (A PRELIMINARY REPORT)

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It is assumed that oxycephaly is due to premature closure and obliteration of the cranial suture lines. This is the consensus of most writers and has been stressed by them since the time of Virchow. Authors have inferred that it was known to Hippocrates and Galen. It is not my intention to enter into a full discussion of the etiologic and pathologic problems and symptomatology. All these phases have been more or less completely covered in a number of papers. The literature is replete with material relating to these aspects of the subject, but only a few cases have been reported in which relief was obtained by surgical means. Skipper, of London, stated in 1934 that "from a survey of the literature it is obvious that the surgical treatment of oxycephaly has seldom been attempted."

I desire, first, to emphasize the pathologic conditions which require treatment in some cases, to discuss briefly operative procedures which have been devised and executed and to describe what I believe to be an original operation for relief from this condition.

Oxycephalic patients who require surgical intervention usually present the same or a similar picture. The sutures of the skull have been prematurely closed, fused and obliterated at a period of life sufficiently early to prevent full growth or development of the brain. As is well known, the growth of the brain takes place at a rapid rate in the early years, and, as a result of the premature closure of the sutures, full development and growth of the brain cannot take place. This results in the following changes: (1) headaches in a number of instances, which may take place at such an early age that they are not recognized; (2) convolutional markings and thinning of the skull, which are readily recognized on roentgenograms; (3) unusual and abnormal irregularities of the skull, due to the fact that the skull is held rigid in some positions and gives way behind the increased intracranial pressure; (4) increase in intracranial pressure, as shown by measurement of the intraventricular pressure and diminution in the size of the ventricles; (5) marked

Read at a joint meeting of the New York Neurological Society and the Section of Neurology and Psychiatry of the New York Academy of Medicine, Nov. 16, 1937. The discussion appears in the transactions of the society published in the April 1938 issue of the ARCHIVES.

bilateral exophthalmos, which may be so extreme and prolonged that loss of the eyes may ensue, and (6) early bilateral papilledema followed by atrophy of the optic nerves, resulting in failing vision or blindness.

In simple language, the intracranial space is too small for the brain, which could and would develop were it not so closely confined within its quarters. This condition is in contrast to that in the microcephalic idiot.

Granted that these statements are true, what can be done to increase the intracranial space in a symmetric manner and, at the same time, to preserve the bony covering and protection of the brain, reduce the exophthalmos and save vision? These are the indications for and purposes of an operation.

OPERATIVE PROCEDURES

Subtemporal Decompression, Unilateral or Bilateral.—This method has been advocated by some writers. It goes without saying that the intracranial space is not increased by this procedure. The skull is not made larger. It is logical to assume that as a result of this operation the intracranial pressure will be decreased, owing to bulging of the brain substance through the sites of decompression. It is also freely admitted that the exophthalmos may recede and vision improve, at least for a while. However, it is not believed that, as the brain develops and increases in size as a result of its growth as well as the ventricular dilatation, the improvement which may follow the operation will continue. Furthermore, the bilateral deformities resulting from the tense bulging through the sites of decompression are undesirable. A considerable portion of the brain on either side becomes vulnerable to grave damage, especially in children.

Lannelongue and Lane advocated a linear resection of the cranium. This operation allowed but slight increase in the size of the skull and surely did not permit symmetric enlargement.

Elschnig recommended resection of the optic canals on the assumption that the canals and foramens are too small. He expressed the belief that the exophthalmos would recede as a result of this operation. It is thought, however, that much benefit cannot be expected, in view of the fact that the marked proptosis or exophthalmos is due to the increase in intracranial pressure rather than to constriction of the optic nerves.

On June 19, 1924, Faber performed what he called "linear craniectomy" on a baby aged 6 months and 7 days. True oxycephaly had not yet developed. The sagittal and right coronal sutures were closed. The lambdoid and left coronal sutures were open, and there was an open metopic suture. He cut two channels in the cranial bones, one to the right of and parallel to the sagittal suture, extending from the right

coronal to the right lambdoid suture, and a second extending from one squamo parietal suture to the other, posterior to the coronal sutures. The bony channels measured about 1 cm. in width. The overlying pericranium was likewise removed. He stated that by August 12 the anteroposterior channel had widened to about 2.5 cm. at the newly created fontanel and that the fontanel pulsated and showed a normal crying impulse. To me this seems to be the most rational operation which heretofore has been offered for relief from the condition.

In 1934 Keegan performed a right temporal decompression with opening of the dura. Herniation of the cortex was marked. Therefore he made bony channels on the right side of the skull, as described by Faber, but did not extend the removal of bone to the left side on account of the condition of the patient. At a later date he removed a circular area of bone, about 5 cm. in diameter, in the left temporal region and cut a channel upward to meet that previously made on the right side. He stated that after operation there was little appreciable separation of the cranial channels, which he thought was due probably to the fact that decompression had been performed on the right side with opening of the dura, but might be due also to the rigidity of the cranial bones.

Bauer, in 1932, advocated a circular resection of the skull in two stages to prevent blindness in cases of oxycephaly. It is assumed that after the operation described by Bauer the upper segment of the skull will rise beneath the scalp flap, owing to increased intracranial pressure, and thus relieve the increase in pressure. With this type of resectional craniectomy symmetry of the head can hardly be attained, owing to the fact that the preexisting deformity or irregularities of the skull will not be corrected because of the stiffness, firmness and fixation of the skull cap. Keegan performed a modification of Bauer's operation on Feb. 1, 1935. He did not complete the resection of the skull, in that it lacked about 3 cm. in the occipital region of being circumferential. He noted no perceptible elevation of the loosened skull cap. On the twenty-sixth day after operation roentgenograms showed no appreciable increase in width of the bone gap in the frontal region from that recorded by a roentgenogram on the tenth day after operation.

In their discussion of the surgical treatment of oxycephaly, Bennett, Keegan and Hunt stated:

> These two cases both present a rather late stage for surgical interference in congenital oxycephaly. It would seem preferable to do a craniectomy for this evident condition during the first year of life when the cranial bones are thinner and more pliable, and before chronic intracranial pressure has produced optic atrophy and threatened loss of vision. Perhaps, also, the dura is thinner at this time and will adjust itself to the growing brain better without the necessity of a decompression opening. At this early age the crucial craniectomy would seem indicated. Later, when the bones become thicker and the ridges more fixed, the circular craniectomy which will permit elevation of the entire skull cap would

seem preferable. A narrow ring of bone may be left in the occipital region for some fixation of the skull cap, or more radical complete separation may be necessary, with additional temporary removal of bone and possibly bilateral subtemporal decompression when vision is seriously threatened.

REPORT OF A CASE

In October 1936, Dr. Philip Wilson, director of surgery at the New York Society for the Relief of the Ruptured and Crippled, requested me to see E. C., a boy aged 8 years, who had been sent to him from Halifax, Nova Scotia, Canada, on account of a malunited fracture of the right femur. He had been admitted to the hospital on August 10.

History.—Delivery had been normal. The patient had had the usual diseases of childhood. At the age of 3 he was knocked down by a truck and was reported to have had an injury to the skull. The details were not known. Ten months before admission he was hit by a car and sustained a fracture of the right femur, for which three attempts at reduction, both open and closed, were made before admission, with the use of anesthesia. He was admitted with the complaint of malunited fracture of the femur with marked anterior lateral angulation and shortening.

Physical Examination.—The boy was fairly well developed, but a little small for his age. Aside from the deformity of the right lower extremity, the outstanding feature was the great degree of bilateral exophthalmos, with drooping of the outer canthi (fig. 1). An external squint was present; there was no ophthalmoplegia. Ophthalmologic examination by Dr. Arthur Knapp revealed swelling of the lids, marked exophthalmos, buphthalmos and 21 degrees of arc of exotropia. The right fundus showed marked pallor of the disk, whereas the left was slightly pink. There was no evidence of papilledema. Vision was definitely impaired. The visual fields were grossly intact. The pupils reacted to light and in accommodation. The boy's mentality was not grossly impaired, but he had a somewhat dull, apathetic countenance. General neurologic examination gave normal results. Lumbar puncture showed increase in pressure to 400 mm. of water; after 30 cc. of fluid was removed the pressure was reduced to 250 mm.; pressure on both jugular veins caused a rise to 650 mm.

Roentgenologic Examination.—Roentgenograms showed the typical changes in a case of oxycephaly, with a high skull, which in the anteroposterior view had a shape not unlike a Gothic arch. Convolutional markings were observed. In the lateral view the convolutional markings (digital impressions) were more apparent, giving a wavy, billowy appearance, like that of fluffy clouds (fig. 2*A*). No suture lines were discernible in either view. The skull showed decided bulging in the former position of the anterior fontanel, with a depression behind it. The skull was much thinner in the middle portion of the vertex than in the anterior, frontal or parieto-occipital regions. The frontal, sphenoid and maxillary sinuses were small. The middle fossa was deep, and the auditory canals were low in position. The sella turcica was rather deep and narrow, with well marked anterior and posterior clinoid processes. The maxilla was small and undeveloped, while the mandible was large and protruding. The optic foramens were oval and of equal size, with smooth walls. Before being aware of the enormous increase in intraspinal pressure, Dr. Irving Pardee recommended encephalographic examination, to be followed by operation, but the type of operation was not designated.

Ventriculograms, made by Dr. W. D. Wingebach, showed general compression of the ventricular system, except for the part of the anterior horns beneath the

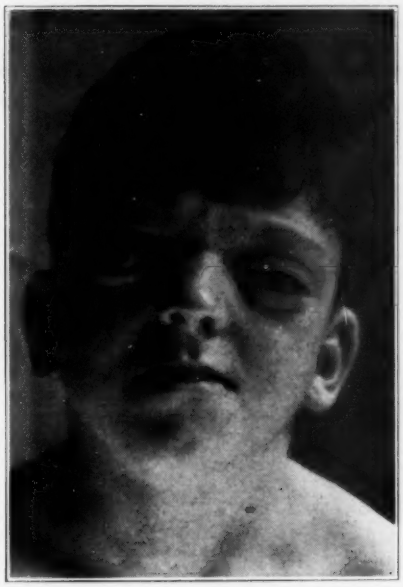

Fig. 1.—Photograph of E. C., a boy aged 8 years, taken on Aug. 9, 1936. The exophthalmos was more marked than appears here. Note the apathetic face, external squint, drooping of the outer canthi, small upper part of the face and large lower jaw.

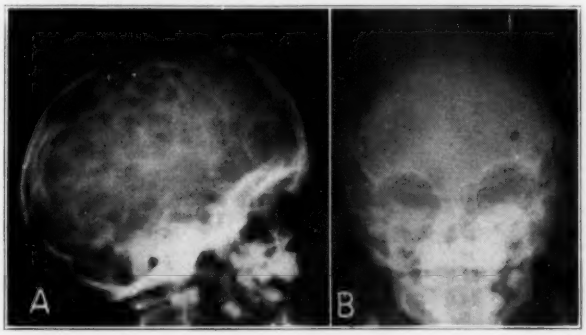

Fig. 2.—Roentgenograms revealing absence of suture lines. *A*, a lateral view, shows the typical thin skull with convolutional markings, due to prolonged increase in intracranial pressure. The middle fossa is deep; the auditory canal is low. All the sinuses are small; the maxilla is small, and the mandible is prognathous. There is marked bulging of the skull at the site of the anterior fontanel. *B*, an antero-posterior view, likewise shows the convolutional markings and the peculiar pointed or rooflike skull.

bulging of the skull in the frontoparietal regions. The intraventricular pressure was greatly increased. Twelve cubic centimeters of cerebrospinal fluid was removed and only 5 or 6 cc. of air substituted.

Considerations Which Determined the Operation.—The question was: How can one enlarge the skull (intracranial capacity) in this case so that the brain may grow, the exophthalmos recede and vision return or cease to fail or the patient not lose his eyes? The cranium should enlarge in a symmetric manner so that the brain can grow upward from the basilar structures. Cutting a groove around the skull would not accomplish this. Neither would cutting in a crosswise direction. These procedures would increase the intracranial space, but not symmetrically.

Creation of large subtemporal decompression sites, with opening of the dura, would result only in bilateral formation of cerebral subcutaneous hernias, which would reduce the pressure but would not increase the actual intracranial space and would not allow the brain permanently to expand and develop.

The ideal, though impossible, condition would be to render the skull elastic and keep it so until the brain had developed and the exophthalmos receded. This could not be done. The next plan was to morsellate the skull in very small pieces, like small tiles, keep them apart until the dura and brain had expanded and then allow the mosaic of small fragments to solidify by regeneration of new interstitial bone.

To make pieces 1 cm. square would be impracticable and take too long. Therefore, it was decided that the fragments of the mosaic, to be formed first on one side of the cranial vault and at a second stage on the other, should be made larger by cutting the bones of the cranial vault into pieces 1½ or 2 inches (3.8 or 5 cm.) on a side and allowing them to separate as a result of the increased intracranial pressure, which would stretch the undulations of the thinned dura (without opening the dura). The spaces between the separated fragments of bone would fill with new bone, which develops between the dura and the pericranium, and so would result in a firm, rounded skull, sufficient to permit symmetric growth of the brain, diminution of exophthalmos and preservation of vision.

The problem was worked out in this manner.

Technic of Operation.—The first operation was performed on the right side on Nov. 10, 1936, with the patient under anesthesia induced with avertin in amylene hydrate and a mixture of nitrogen monoxide, oxygen and ether. A horseshoe-shaped incision in the scalp, including most of the right side, was made as follows (fig. 3): Beginning just in front of the temporal artery in front of the ear, the incision was carried upward, forward and inward across the forehead, about 1½ inches (3.8 cm.) above the right eyebrow, to the midline, then along the midline backward, almost to the external occipital protuberance, and downward, outward and forward in front of the position of the lateral sinus to a point just above the mastoid process, leaving a pedicle in the temporal region.

The entire scalp flap was turned downward, exposing the right side of the skull, exclusive of the cerebellar region. The flap consisted of the scalp, galea, temporal fascia and muscle and pericranium. Bleeding from the flap was controlled by a pedicle clamp, especially designed. Bleeding from the rest of the scalp margins was controlled with skin clips. No suture lines were seen. Burr holes were made about the periphery of the exposed skull about 2 inches (5 cm.) apart, and several other burr holes were made in the central part of the exposed skull.

The thickest portion of the skull in the upper, parietal, occipital and frontal regions was about ⅛ inch (3 mm.). The bone in the lower part of the temporal region was very thin and could be bent. It was from about 0.5 to 1 mm. thick,

and offered little more resistance than a small parchment lamp shade. It was thought that the "grooving" between the fragments should be done with a deVilbiss bone forceps. The one used measured 3/16 inch (4.7 mm.) in width. A slightly wider forceps may be advisable.

After all the burr holes had been made, a bone flap near the midline was outlined, with the base still attached above in the parietal region near the midline; that is, the bone was cut anteriorly, below and posteriorly, making a flap about 2 by 2½ inches (5 by 6 cm.), which was left attached toward and near the midline. As soon as this had been done, two observations were made: 1. The distal free end of the bone flap moved up and down with pulsation of the brain, like a spring-board, while the base of the flap and the remainder of the skull were fixed. 2. The

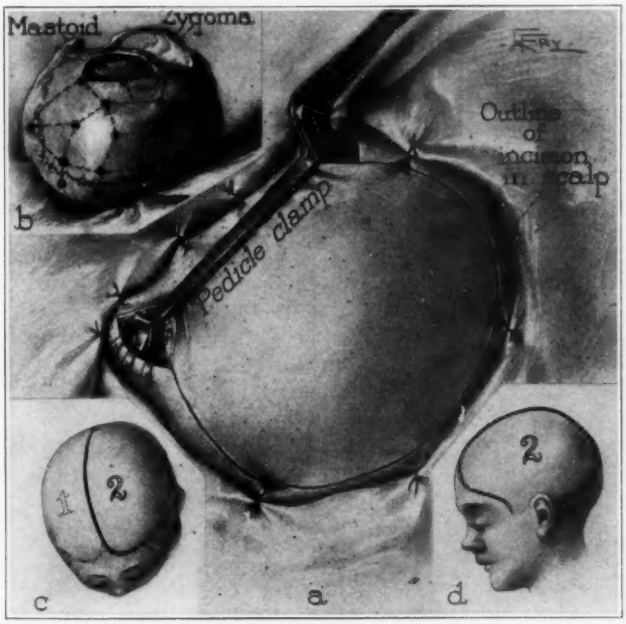

Fig. 3.—Drawing showing position of the incisions. In *a* the incision is outlined throughout and completed at the base of the flap. Bleeding from the scalp and muscular flap is controlled by a specially designed pedicle clamp. In *b* the position of the burr holes and fragments of skull is indicated. In *c* and *d* scalp flaps are outlined.

thinned dura bulged upward between the grooves in the bone in a manner similar to that in which a cloth on which two planks have been placed about 1 inch (2.5 cm.) apart bulges or protrudes between the planks when they are shoved together. The dura was thin, transparent and redundant.

These observations showed that the brain was under such marked compression that it would expand if given an opportunity, that the sum total of intradural space was relatively greater than the sum total of the intracranial space and all that was needed was to make a mosaic of the bones of the skull sufficient to allow filling of the thin, redundant dura. (In the usual skull the dura does not protrude upward into the groove made by the deVilbiss forceps.)

From these observations it was believed that I was on the right track. Therefore, one hole was connected with another until the right side of the skull was cut into rectangular and triangular pieces of bone, measuring from about 1¾ to 2 inches (4.5 to 5 cm.) or more on a side. The only exception was a rather large oval defect, longer in the horizontal direction, made in the thin area of the squamous portion of the temporal bone. The dura was not opened.

Care must be taken in cutting the pieces of bone, else a fragment is easily dislodged and may fall to the floor and create confusion. Therefore, it is advisable to cut through from one hole to another, leaving a small interval of bone holding the fragments together until most of the work is done (fig. 4). Then the small interval of bone can be cut through and covered with the scalp flap before a

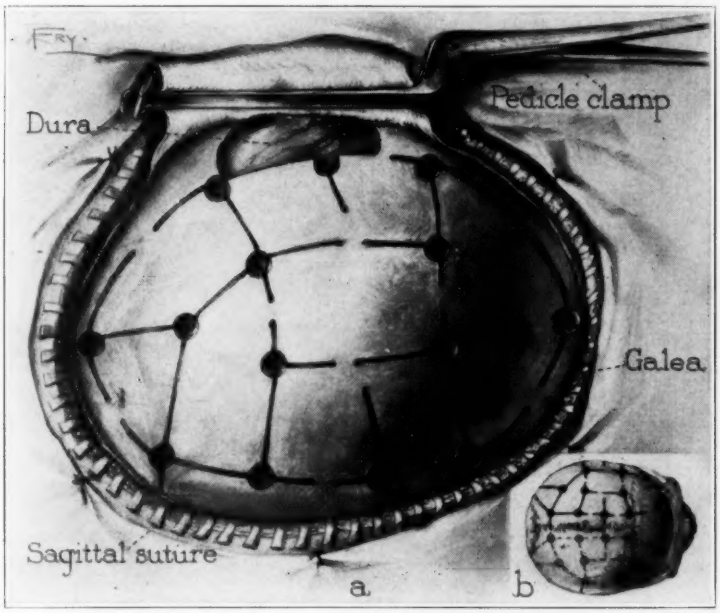

Fig. 4.—In *a* the flap is reflected; bleeding from the flap is controlled by a pedicle clamp, and that from the margins of the scalp, by skin clips. A mosaic of the left side of the skull has been made by cutting between burr holes with a deVilbiss forceps. The fragments of bone are held together by a narrow bridge until the last part of the operation, in order to prevent displacement and loss of a segment of bone. The inset, *b*, indicates the position of the burr holes and connecting grooves on both sides of the cranium. The operation was performed on the left side two and one-half months after that on the right.

fragment is dislodged from the dura. The attachment to the dura is meager for the most part.

It was surprising to observe how widely the fragments of bone separated one from another. They spread apart like the opening of one's fingers. The cut made by the deVilbiss forceps increased in width from 3/16 to ¼ inch (4 to 6 mm.) or more in some places (fig. 5). The peripheral pieces of bone were considerably

elevated above the fixed margin of the skull. There was little bleeding. The scalp flap was returned to its position over the morsellated fragments of skull, and was closed without drainage with two layers of interrupted sutures of silk, one for the galea, muscle and fascia and one for the scalp (fig. 6). A copious dressing covered with a plaster shell was applied.

After completion of the scalp suture, two observations were made: 1. One could readily note the difference in the rotund appearance of the right side, or site of operation, and the rooflike appearance of the left, or intact, side. 2. Just as the operation was completed, and before the drapes were removed, I peered beneath the anesthetist's shield. Somewhat to my surprise, and to my great pleasure, the right eyeball had sunken into the orbit as if it had been pushed back or "stepped on." The exophthalmos of the right eye had almost disappeared. That on the left

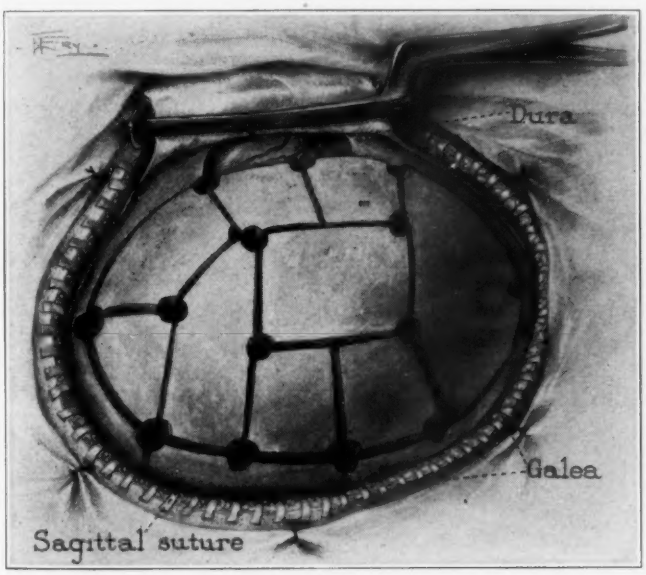

Fig. 5.—Illustration showing completion of grooves between the burr holes, making the mosaic of skull fragments. The entire mosaic was lifted well above the margin of the skull by the increased intracranial pressure exerted on the very thin dura. The spaces between the fragments widened more than is shown in the illustration. The removal of bone and the thinning of the squamous portion of the temporal bone were greater than are shown. The dura was not opened.

side (opposite the site of operation) had considerably diminished, but not to the same degree as on the right.

A small transfusion was given on the table, and the patient was returned to his bed in good condition.

It is not known just how large one should make the individual pieces of skull. They should be sufficiently small to allow the skull to assume a proper symmetric shape. It is possible that larger sections of the skull would suffice. It goes without saying that the length of time required for making larger sections would be less than that for smaller ones.

It is also likely that in a number of cases the operation will be required at a much earlier age than in the case reported, in order to prevent loss of vision and other disastrous effects. Writers have reported cases in which blindness took place within the first three years of life. Since such young children do not withstand prolonged operations well, it is believed that making the mosaics of skull fragments in either one or two stages could be more quickly effected by extending an incision from one temporal region across the vertex to the other (autopsy incision), maintaining exposure and controlling hemorrhage by means of angulated self-retaining retractors and cutting the grooves from one burr hole to the other with a motor-driven osteotome. It is believed that the segments of thin skull could be more quickly made with the osteotome than with a deVilbiss forceps.

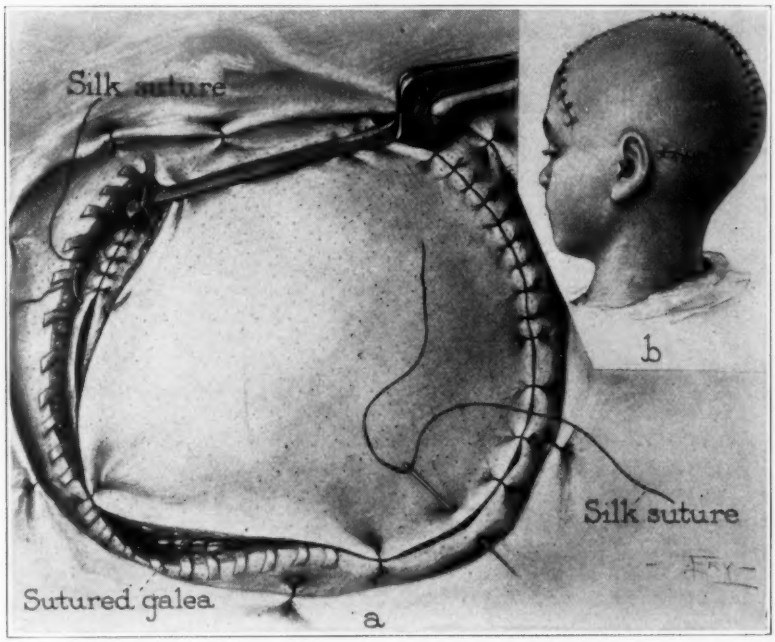

Fig. 6.—Illustration showing closure of incision without drainage.

Progress.—Most of the sutures were removed on the third day, and the remainder, on the fifth. The incision healed kindly.

The exophthalmos disappeared on the right side and was markedly lessened on the left. The patient's general condition improved. He stated that he could see better. The right side of the head felt like a linseed poultice, soft and doughy. After two weeks there was a definite sensation of solidification on palpation. After five weeks the skull was definitely fixed and resistant on the right side. During this interval a plaster helmet was worn for protection.

Roentgenograms of the skull on Dec. 7, 1936, showed the lines resulting from cutting the skull on the right side into reasonably small fragments (fig. 7*A*). They gave a bizarre effect, similar to "Martian canals." The widened interstices between the fragments of bone were being filled with new bone. The skull on the right side was definitely more rounded than on the left, and the fragments of

bone were elevated above the margin of the skull. In the anteroposterior view, the distance from the midline to the midtemporal region on the right side was 8 cm. On the left side the distance was 6.8 cm., a difference of 1.2 cm.

Operations for straightening the femur were performed on August 12 and December 2, with the patient under anesthesia induced with a mixture of nitrogen monoxide, oxygen and ether and ethyl chloride and ether.

On Jan. 26, 1937, a procedure similar to the one described was carried out on the left side of the skull, anesthesia being induced with avertin in amylene hydrate and a mixture of nitrogen monoxide, oxygen and ether. After morsellation (boring of burr holes, cutting into fragments and removal of thinned bone in the temporal region), there remained a strip of bone in the midline, directly over the longitudinal sinus, about 1 inch (2.5 cm.) wide in the middle and broadening at either end. It

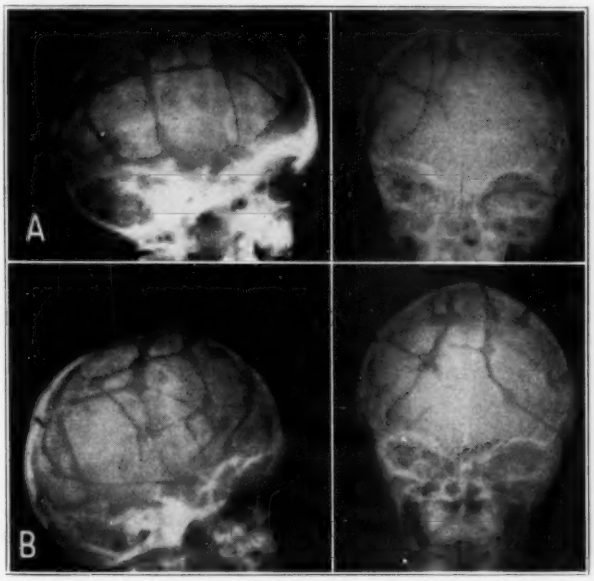

Fig. 7.—*A*, roentgenograms made on Jan. 26, 1937, two and one-half months after the first operation. The grooves between the fragments are wider than when made. The lateral view shows the position of the skull fragments making a mosaic, and the anteroposterior view, the increase in size of the right side of the skull, with elevation of the fragments of bone and a contour rounder than that on the left. Convolutional markings have almost disappeared. *B*, roentgenograms made on February 3, one week after the second operation. By comparing them with the roentgenograms shown in figure 2, one can readily appreciate the difference in the shape, size and contour of the skull.

reminded one of a basket handle, extending down the middle of the skull over the longtitudinal sinus. If this were not divided, there could be no expansion in the anteroposterior direction. Therefore, two grooves were cut across this bony ridge, one in the occipitoparietal and one in the frontoparietal region. (Probably three transverse divisions—frontal, parietal and occipital—would be better. The three grooves would allow more expansion than two.) The bone forceps passed

readily over the longitudinal sinus, without damage. The groove for the sinus was shallow, and the sinus was not firmly adherent. Observations made on the left side were similar to those on the right with respect to the separation and elevation of the fragments of bone.

Roentgenograms made on February 3 showed that the transverse diameter of the skull was much increased (fig. 7 *B*). In the lateral view one could see that the middle section of the bone in the midline between the two transverse cuts over the longitudinal sinus was elevated and the deformity was corrected. New bone was filling the grooves on the right side. Convolutional markings were practically absent on the right side two months and three weeks after the operation. They were still present on the left side.

The postoperative ophthalmologic report by Dr. Arthur Knapp was as follows: "Reexamination on March 9, 1937, after completion of surgical treatment, mani-

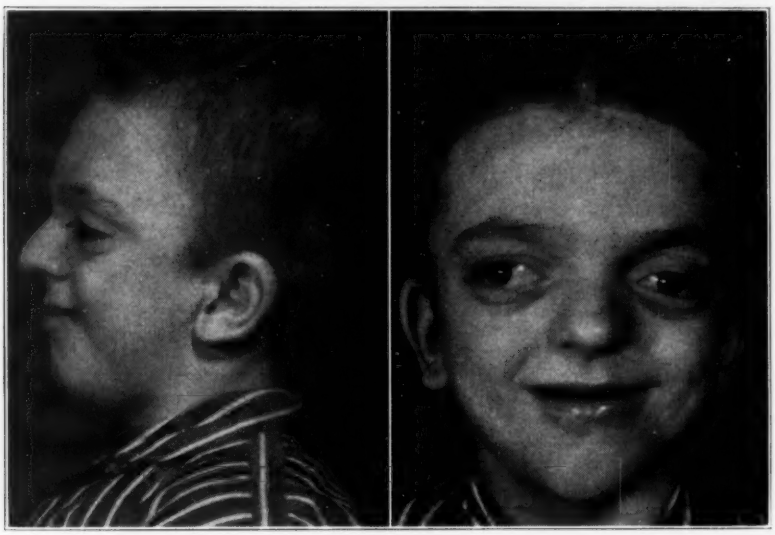

Fig. 8.—Photographs of the patient made on March 2, thirty-five days after operation on the left side.

fested several changes. Vision was much improved. Swelling of the lids and exophthalmos had receded greatly. There was 35 degrees of arc of exotropia with 3 degrees of arc of right hypertropia. Both optic disks had lost a great deal of their pallor. The nerve head of the right eye was only slightly pink, while that of the left appeared normal."

The boy made an uneventful recovery. He returned to Halifax during the summer, after the malunion of the right femur had been corrected by Dr. Wilson. The head had a normal rounded contour. The fragments of bone on both sides of the cranial vault were firmly united. The apathetic appearance had changed to one of alertness (fig. 8). Vision, which originally was so poor that the patient could see one only about the bed, had improved so much that he could recognize one when he entered the assembly hall, at a distance of 100 feet (30.5 meters) or more. He took an active part in the children's play in the ward.

The patient recently returned to the hospital for correction of the squint by Dr. Knapp.

This is only a preliminary report, and it is well known that "one swallow does not make a summer." It is expected that the patient will be followed. It is hoped that a later and favorable report can be made.

SUMMARY

1. True oxycephaly, which is believed to be due to premature closure of the cranial suture lines, is likely to result in blindness, owing to prolonged and marked increase of intracranial pressure with final atrophy of the optic nerves. Extreme exophthalmos may result in loss not only of vision but of the eyeballs.

2. The operations which have been advised for this condition are briefly discussed. These procedures include subtemporal decompression, unilateral or bilateral; the linear resection of Lannelongue and Lane; resection of the optic canals as recommended by Elschnig; the linear craniectomy of Faber; circular resection of the skull as advocated by Bauer, or a combination of these procedures. It is not believed that any one of these operations will permit symmetric expansion and growth of the skull and brain, although temporary relief from the exophthalmos and defective vision may result.

3. A new operation, performed in two stages, consisting of making a "mosaic" of the bones of the cranial vault is advocated and described. It is possible that the operation may be performed at one session through an "autopsy incision," especially in the case of infants.

4. A case of typical oxycephaly associated with extreme exophthalmos, increase of intracranial pressure and failing vision, in which this operation was performed, is described in a preliminary report.

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Case Reports

CEREBRAL ANGIOMA ARTERIALE

A Case in Which Migrainous Headache Was the Earliest Manifestation

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Tumors of the blood vessels of the central nervous system, although relatively uncommon, have aroused increasing interest among pathologists and clinicians in recent years. Inaccurate pathologic differentiation had caused much confusion with regard to them until Cushing and Bailey,[1] in 1928, published a clinicopathologic study of the tumors of the blood vessels of the brain which helped to clarify the subject. They classified such tumors under two broad headings: (1) true neoplasms (hemangioblastomas), which occur most frequently in the cerebellum, and (2) angiomatous malformations, which may be chiefly capillary (telangiectasis), venous (angioma venosum) or arteriovenous (angioma arteriale) in composition.

The angiomatous malformations of clinical importance are the venous and arteriovenous angiomas. They are situated in the cerebral hemispheres and are primarily surface lesions. Cushing and Bailey estimated that they comprise about 1 per cent of all intracranial tumors. They show no predilection for any particular lobe, and their incidence is about the same in the two sexes. Among the common clinical manifestations of the supratentorial angiomas are epilepsy and hemiplegia. The venous angiomas usually produce symptoms in childhood, but the nature of the lesions may not be suspected unless nevi of the skin are present. These nevi may be extensive, but frequently are confined to the distribution of the trigeminal nerve on the same side as the cerebral lesion.[2] Congenital abnormalities of the ipsilateral eye, such as buphthalmos, heterochromia iridis, coloboma of the disk or high refractive error, may also be associated.[3] The arterial angiomas do not usually

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1. Cushing, H., and Bailey, P.: Tumours Arising from the Blood Vessels of the Brain, Springfield, Ill., Charles C. Thomas, Publisher, 1928.

2. (*a*) Weber, F. P.: A Note on the Association of Extensive Haemangiomatous Naevus of the Skin with Cerebral (Meningeal) Haemangioma, Especially Cases of Facial Vascular Naevus with Contralateral Hemiplegia, Proc. Roy. Soc. Med. **22**:431, 1929. (*b*) Cushing and Bailey.[1]

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cause symptoms until the second or third decade. Recognition of these lesions clinically depends on the finding of audible intracranial bruits and secondary extracranial effects of the arteriovenous communications.

In the following case of cerebral angioma arteriale the correct diagnosis and localization of the lesion were made on clinical examination and verified by postmortem examination. The clinical and pathologic features of the case are considered in detail, and an attempt is made to explain the principal symptoms, notably, headaches of a migrainous type and epilepsy, on the basis of the pathologic changes.

REPORT OF CASE

History.—Miss A. L., aged 26, who was admitted to the Toronto General Hospital on April 18, 1936, had been subject since childhood to periodic headaches of a throbbing character. These were always on the right side, occurred usually at intervals of from two to three weeks and lasted from several hours to a day. During the three years prior to admission the headaches had increased in severity and frequency. They were brought on and aggravated by excessive use of the eyes and exposure to strong lights and bright sunshine. The patient had stopped reading and sewing because they tended to bring on headaches. For a short time before the onset of a headache she usually noted spots dancing before the eyes, but no history of well formed visual hallucinations was elicited. Nausea often accompanied the headaches, but vomiting was rare. Several hours of complete rest in bed with the eyes closed was the only measure effective in giving relief. Occurrence of the headaches had no constant relation to the menstrual cycle.

During the past four years she had suffered from attacks which occurred when she was active during the day, and frequently they followed some extra exertion. Each attack was ushered in by a sensation of numbness starting in the hands and spreading up the arms to the chest and neck. About ten minutes after the onset of the paresthesia she lost consciousness. After about five minutes consciousness was usually regained, and the patient felt weak and drowsy and had a headache, which was relieved only by several hours' sleep. Her friends stated that she sometimes emitted a cry or groan prior to losing consciousness; no convulsive movements of the limbs or jaw had been noted, however, and she had never bitten her tongue or been incontinent. The attacks occurred at intervals of two or three months until four weeks before admission, since when there had been an average of one each week. For eight months she had been taking ¾ grain (0.4 Gm.) of phenobarbital twice daily, without any apparent effect on the frequency or severity of the attacks. Bromides in varying doses were also administered for a time, but were likewise ineffective.

The patient complained of a buzzing sound in both ears, which had been present for many years. She was unable to state when it had first developed, but in recent years it had become gradually more marked. She was in the habit of pressing her hands to her neck, as she had discovered that pressure at the sides lessened the intensity of the sound. She had experienced sensations of fulness of the neck and of pressure in the throat during the past year.

During the past two years she had noted some impairment of memory and difficulty in thinking. She expressed the belief that her strength and energy were failing, although there had been no loss of weight or appetite. There was no impairment in vision or hearing.

The patient had been born in Finland. She had come to Canada in 1929 and was employed as a domestic until two years before admission to the hospital.

when she was discharged because of the attacks. Except for the symptoms recorded, the patient enjoyed excellent health. She had suffered from no serious illnesses. Her parents and 5 siblings were all alive and well. No history of epilepsy or migraine in the family was obtained.

Examination.—The patient was well developed and well nourished. She was intelligent and cooperative. No gross defect in memory, perception or attention was noted. Emotionally she was stable.

Auscultation of the skull revealed a loud bruit synchronous with the pulse beat. This was most intense over the temporal and occipital regions on the right side. The sound could also be heard faintly over a similar area on the left side of the skull, but was scarcely audible over the vertex. Repeated observation failed to show much variation in the intensity of the bruit with varying degrees of visual stimulation, although on one occasion, after the patient had been sleeping for

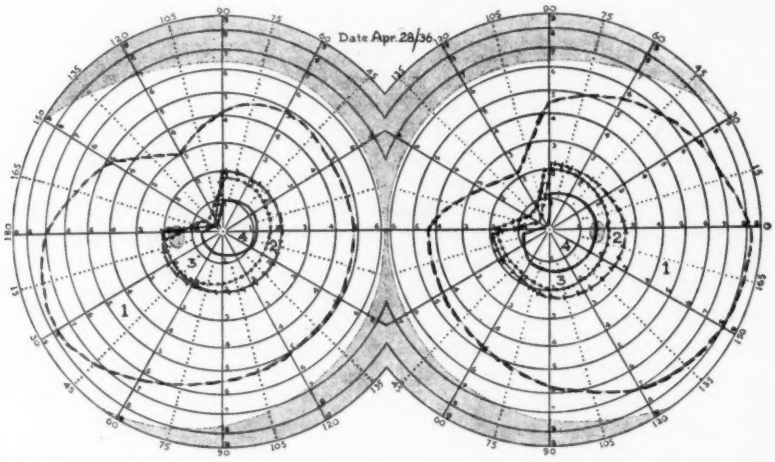

Fig. 1.—Perimetric chart of the visual fields. *1* indicates the field for white; *2*, for blue; *3*, for red, and *4*, for green, taken in daylight with test objects 5 mm. in diameter, at a distance of 330 mm., with good cooperation of the patient. Visual acuity in the right eye was 6/6, and that in the left, 6/9.

several hours, the sound was less easily heard than usual. When headache was present no definite difference in the audibility of the bruit was observed as compared with that in the intervals of freedom from headache. Pressure on each carotid artery separately caused no appreciable change in the bruit, but pressure on both carotid arteries simultaneously abolished it subjectively and objectively.

Examination of the fundi revealed nothing abnormal. The visual acuity was 6/9 in the left eye and 6/6 in the right eye. Examination of the visual fields showed a well marked defect occupying the upper quadrant of the left homonymous fields (fig. 1). Movements of the eyes were full, but extreme lateral conjugate deviation of the eyes to the right could not be sustained for more than a few seconds. The patient stated that holding this position of the eyes was a great effort, because it caused a feeling of fatigue and acute discomfort in the right eyeball.

Examination of the remaining cranial nerves revealed nothing of significance. Examination of the limbs for power, tone and coordination likewise revealed no abnormality. There were no alterations in the reflexes. There was slight subjective diminution in sensation to pinprick over the left side of the body as compared with that on the right, but otherwise sensation, superficial and deep, was not disturbed.

Examination of the ears, nose and throat, heart, lungs and abdomen revealed nothing abnormal. The blood pressure was 128 systolic and 72 diastolic.

Laboratory Findings.—Urinalysis and hematologic examination revealed nothing abnormal. The Wassermann reaction of the blood was negative. Roentgenographic examination of the skull showed the venous markings to be unusually prominent, particularly on the left side. An area of absorption of bone was present in the right middle cranial fossa. This area, about 2 inches (5.08 cm.) in diameter, extended backward from the region of the sella turcica (fig. 2). On May 18 roentgenograms were made after the injection of colloidal thorium dioxide into the right common carotid artery. The plates were unsatisfactory, owing to underexposure.

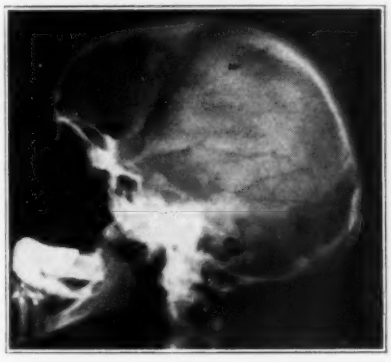

Fig. 2.—Lateral roentgenogram of the skull taken from the right side to show erosion of the petrous portion of the right temporal bone and of the right middle cranial fossa by overlying tumor tissue. The photograph also shows widening of the vascular grooves in the lateral wall of the skull.

Clinical Diagnosis.—The clinical diagnosis was cerebral angioma situated at the base of the brain on the right side, involving the inferior part of the right optic radiation.

Progress.—During her three months' stay in the hospital, the patient remained almost entirely in bed. She received no phenobarbital, but had no seizures of any kind. She complained of severe headaches about once a week, which were benefited by sleep induced by sedatives.

After discharge from the hospital on June 23, she attempted to assist with housework and to go out occasionally. The seizures recommenced soon after she began taking mild exercise. These now included severe grand mal convulsions without any warning, as well as the minor attacks with an aura of numbness in the upper limbs and chest, similar to those previously described. The seizures gradually increased in frequency and severity. One grain (0.6 Gm.) of phenobarbital twice a day was prescribed, but, as before, it failed to affect the attacks in any way.

On Sept. 21, 1936, she was admitted to the hospital, deeply unconscious. While walking along the street two hours previously, she had fallen suddenly, apparently in a convulsive seizure, striking her head on the pavement.

Examination on admission showed her to be comatose, with Cheyne-Stokes respiration. The pulse was regular and the rate 60 per minute; the blood pressure was 130 systolic and 90 diastolic. There was ecchymosis in the region of the left eye. A recent hemorrhage was seen in the right retina, close to the disk. The right pupil was widely dilated and did not react to light. There was weakness of the right side of the face. The left arm and leg were spastic, with increased reflexes and dorsiflexion on plantar stimulation of the left foot; the abdominal reflexes were absent.

The cerebrospinal fluid was under markedly increased pressure and contained gross blood. Twenty cubic centimeters of fluid was allowed to drain off slowly.

After this procedure the respirations temporarily improved, but there was no sign of returning consciousness. The bruit was of the same character and intensity as before, except that it was now heard equally well over the two sides of the skull.

About eight hours after admission the patient's condition suddenly became worse. She was deeply cyanosed, and respirations were very irregular. Spinal drainage was repeated, but without any appreciable effect. Respirations ceased nine hours after admission.

Postmortem Observations.—The observations of particular interest in this case were confined to the brain. Those not relevant to the lesion under discussion will be dismissed briefly.

The body was that of a well developed white woman, weighing 175 pounds (79.4 Kg.) and measuring 63 inches (160.02 cm.) in height. Examination of the skull showed two fractures, one in the left middle cranial fossa, which had torn the anterior branch of the middle meningeal artery, and the other a thin crack in the left side of the cribriform plate of the ethmoid bone. A large extradural hemorrhage was present in the anterior part of the left middle cranial fossa. In the posterior part of the right middle fossa the bony floor was extremely roughened and eroded, and the dura here was firmly adherent to both the bone and the brain. The vascular grooves in the bony cranium were extremely deep, particularly on the left side.

The brain weighed 1,465 Gm. There was a diffuse subdural hemorrhage over both hemispheres. A slight subarachnoid suffusion was present on the right side; it was entirely in the region of the lateral and inferior surfaces of the posterior part of the right temporal lobe and the anterior part of the right occipital lobe and corresponded to the area in which the dura was adherent to the floor of the right middle cranial fossa. The basal cerebral arteries had thin, flexible walls, and their distribution and size were not remarkable, except that the right posterior cerebral artery was larger than the left; since the posterior communicating artery was of normal size, it was assumed that the right posterior cerebral artery supplied a considerable quantity of blood to the tumor about to be described.

The inferior portion of the right temporal and occipital lobes was occupied by a tumor (fig. 3). Its surface was stringy and fibrous and firmly adherent to the upper surface of the right side of the tentorium cerebelli. Toward its lateral margin the posterior part of the tumor was incorporated with the right lateral sinus. The tumor tissue was reddish and hemorrhagic and contained a few small white patches. It replaced the cortical tissue over an area which measured 7.5 cm. anteroposteriorly and 4 cm. transversely; it extended slightly over the inferolateral border of the right temporal lobe on to its lateral surface.

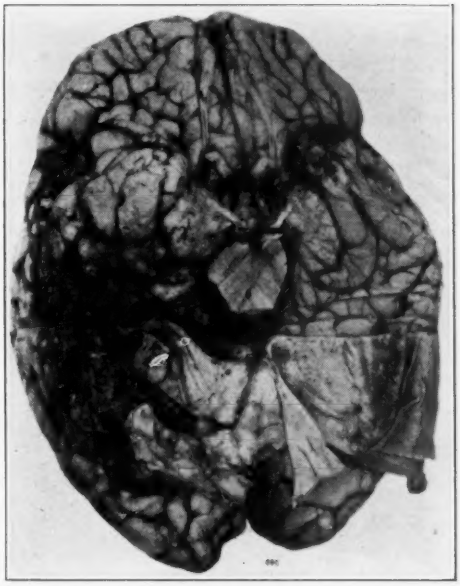

Fig. 3.—The brain viewed from below after removal of the cerebellar hemispheres and brain stem. The under surface of the right temporal and occipital lobes in their outer parts is seen to be invaded and destroyed by a mass of firm, tough, extremely vascular tissue. A portion of the tentorium cerebelli is visible, to the upper surface of which tumor tissue is adherent. A patch of subarachnoid hemorrhage is visible at the tip of the left temporal lobe. The inferolateral border of this lobe in its anterior part is seen to be flattened by compression of the underlying extradural blood clot caused by rupture of the left middle meningeal artery.

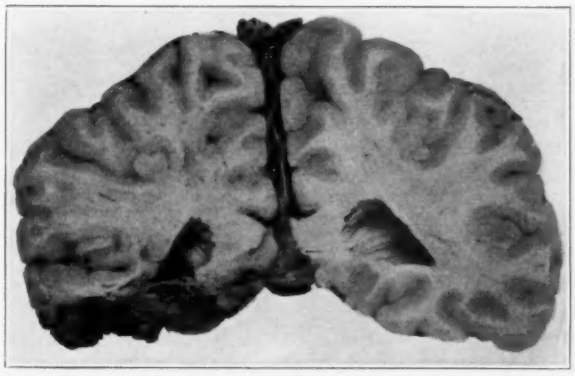

Fig. 4.—Vertical section through the posterior parts of the temporal lobes, showing the tissue of the angioma infiltrating and destroying the cortical tissue and the underlying white matter on the inferior surface of the right temporal lobe. The variability in size of the vascular channels is well demonstrated, and numerous hemorrhages can be seen in the tissue between the vessels. The tumor encroaches on the floor of the descending horn of the right lateral ventricle, but the overlying ependyma is intact.

A vertical section of the right cerebral hemisphere just posterior to the midbrain (fig. 4) revealed a tough, firm mass of tortuous vascular channels, replacing the cortical tissue and white matter to a depth of 1 cm. The tumor showed no invasive characteristics, and, though it replaced the tissue of the floor of the descending horn of the lateral ventricle, it did not invade the cavity; the choroid plexus was not involved.

The spinal cord showed numerous small calcareous plaques in the arachnoid membrane and a moderate amount of hemorrhage in the subarachnoid space. There was no evidence of inflammatory change or invasion by tumor in any area.

Microscopic examination of the tissue composing the tumor showed numerous, closely placed, large and small blood channels, the majority of which resembled veins. The walls of a small proportion of the vessels were thickened and seemed

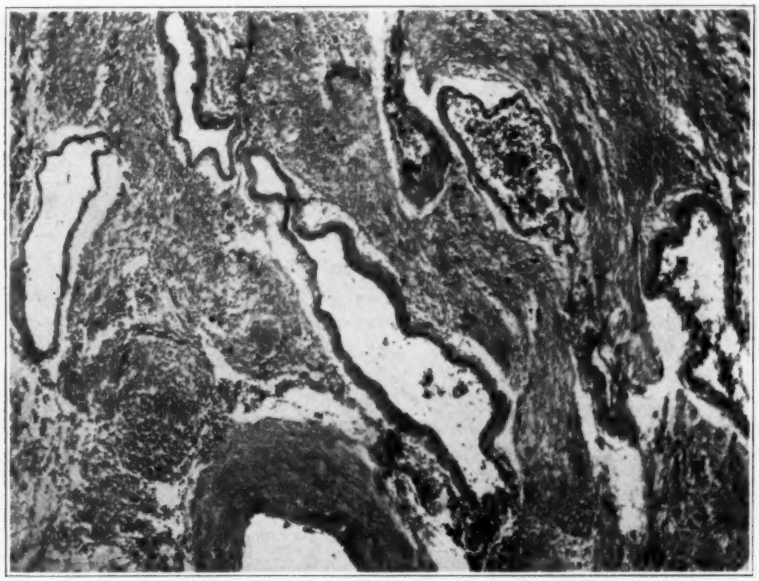

Fig. 5.—A photomicrograph of the tissue of the angioma, showing the irregular vascular channels. The varying thickness of the walls of the vessels is demonstrated. Numbers of circulating red corpuscles are seen in the lumens of the vessels of the varix. The large channel in the lower part of the photograph has a thick wall, mainly composed of fibrous tissue. The glial tissue between individual vessels is best seen in the upper part of the photograph.

to represent faulty attempts at arterial structure (fig. 5). These various vessels were matted together by an interstitial connective tissue in which varying quantities of glial fibers could be demonstrated, although in some places they were extremely few. Irregularly scattered throughout the mass were a few small patches of hemorrhage into this interstitial tissue. There was no evidence of proliferation of any given cell type, in either a benign or a malignant fashion.

The abdominal cavity appeared to be normal in all respects, and the various viscera lay in their usual positions. Examination, both macroscopic and microscopic, of each organ revealed no significant lesions. The heart and lungs lay

in the thorax in their normal relationship, but the lungs were somewhat boggy in consistency, though freely crepitant. Their cut surfaces were extremely moist and exuded a considerable quantity of pink, frothy fluid. The heart weighed 365 Gm.; the epicardial and endocardial surfaces, valve leaflets and orifices, coronary arteries and myocardium were all free from pathologic changes.

COMMENT

Clinical Symptoms.—The principal signs leading to the clinical diagnosis were the bruit heard on auscultation of the skull and the defect in the visual fields detected by perimetry. The homonymous defect in the left superior quadrants of the visual fields (fig. 1) was indicative of the extent to which the inferior portion of the right optic radiation was encroached on by tumor (figs. 3 and 4).

Cushing and Bailey [1] stated that an audible intracranial bruit, when coupled with increased extracranial vascularity, is the most likely element on which a correct clinical diagnosis of angioma arteriale may be based. However, as they pointed out, a bruit is not always present in these cases, and even when present may be a most variable symptom. Again, audible intracranial bruit may be associated occasionally with meningiomas and certain vascular gliomas. Except in rare cases of these tumors and in those of the traumatic arteriovenous fistulas, the presence of a bruit is almost always indicative of an angioma arteriale. Evidence of increased extracranial vascularity of the head and neck was not observed in this case, nor was there cardiac hypertrophy. The patient had complained of a sense of fulness in the neck during the past year, but the pulsations of the carotid arteries did not appear unusually prominent. Abolition of the bruit (subjectively and objectively) after compression of both carotid arteries was of interest. The tumor was in the distribution of the right posterior cerebral artery, and compression of both carotid arteries shut off the main source of blood supply to the anterior part of the circle of Willis. Immediate compensation would be expected by the blood from the vertebral arteries, via the basilar artery, becoming largely diverted from its normal course through the posterior cerebral arteries to flow through the rest of the circle of Willis and supply the middle and anterior cerebral arteries. The increased size of the right posterior cerebral artery suggests that the vascular demands of the tumor were large, and it is not surprising that the bruit was temporarily abolished when the flow was materially lessened.

From their onset, the headaches occurring in this case were probably caused by the angioma, but, despite the absence of a history indicating a familial tendency, certain features suggested a diagnosis of migraine. The headaches had been present since childhood and were consistently confined to the right side of the head. The bouts occurred at intervals and on most occasions were preceded by subjective visual disturbance. Profuse lacrimation of the right eye frequently accompanied the headaches.

A case of verified cerebral hemangioma in which there was a long history of periodic headaches of a migrainous type preceding the onset of other symptoms was described by Alajouanine, Petit-Dutaillis and

Monbrun.[4] Baruk [5] reported a case of unverified cerebral angioma in which migraine was the earliest manifestation. Since cerebral angiomas are primarily surface lesions and are therefore in intimate contact with the meninges, it is not surprising that headache should be an early and prominent symptom in cases of this tumor. Observations by neurosurgeons have indicated that the blood vessels and perivascular tissue of the meninges are the main intracranial sites where painful sensations can be initiated by stimulation. Studies on headache produced experimentally by injection of histamine have shown that the intensity of the headache is proportional to the degree of dilatation and stretch of the intracranial vessels and perivascular tissues, and there is good evidence that the pial and dural arteries and their surrounding tissues are primarily responsible for the headaches.[6] This is in accord with the conception of migraine as a functional disturbance in the autonomic control of the cerebral arteries, the headaches resulting from local vasodilatation in the meninges.

From the history, it appeared that the most important factor in the production of the headaches in this case was strong or prolonged visual stimulation. It is probable that this was determined by the site of the lesion, which encroached on the right optic radiation. If it can be assumed that strong visual stimuli are associated with increased vascularity of the visual cortex, it might be possible to explain the headaches on the basis of increased blood flow transmitted to the vessels of the tumor, leading to compression and distortion of vessels in the portion of the meninges which was observed to be adherent to the tumor and to the base of the skull. This explanation would account for the consistency in the location and character of the headaches which had prevailed since they commenced in childhoood.

Experimental and clinical evidence is available which lends support to the foregoing suggestion. By means of plethysmography and measurements of the difference in oxygen content of the blood entering and that leaving the brain, Alexander [7] secured evidence of dilatation of the cerebral vessels when the optic nerve was stimulated by a strong light thrown on the retina. Fulton [8] reported a case in which a circumscribed angioma arteriale racemosum of the left visual cortex had been verified at operation. A decompression was made, but there was no attempt to remove the tumor. Incomplete right homonymous hemianopia

4. Alajouanine, T.; Petit-Dutaillis, D., and Monbrun, P.: Tumeur occipitale (hémangiome de la faux du cerveau) avec long passé de migraines ophthalmiques: Hémianopsie en quadrant inférieur ayant rétrocédé complètement après ablation de la tumeur, Rev. neurol. **1**:111, 1932.

5. Baruk, H.: Migraines d'apparence psychogénique suives d'épilepsie jacksonienne dans un cas d'angiome cérébral, Encéphale **26**:42, 1931.

6. Clark, D.; Hough, H., and Wolff, H. G.: Experimental Studies on Headache: Observations on Headache Produced by Histamine, Arch. Neurol. & Psychiat. **35**:1054 (May) 1936.

7. Alexander, F. G.: Untersuchungen über den Blütgaswechsel des Gehirns, Biochem. Ztschr. **44**:127, 1912.

8. Fulton, J. F.: Observations upon the Vascularity of the Human Occipital Lobe During Visual Activity, Brain **51**:310, 1928.

and a well marked bruit were found on examination. When the patient was at rest with the eyes closed, the bruit was distant and weak. After he used the eyes for reading or attempted to see objects on the blind side, without otherwise exerting himself, a marked increase in the bruit occurred, detectable both by auscultation and by electrophonograms. Other types of mental effort had no influence on the bruit. Fulton concluded that in his case visual effort was associated with increased vascularization of the occipital cortex. Changes in the intensity of the bruit, following ordinary visual stimulation, were not carefully sought in our case, but on one occasion, after sleep, the bruit was noted to be less audible than usual. One observation such as this cannot be regarded as significant, but the statement of the patient that several hours of complete rest with the eyes closed was the only effective method of gaining relief from the headaches is more important. The patient did not attribute the onset of headaches to physical exertion; so it is improbable that the relief obtained from rest was associated with the lessened circulatory rate. That sleep does not result in decreased blood flow through the brain was shown by the work of Gibbs and his co-workers.[9] These authors demonstrated that no significant change occurs in the volume of blood inside the skull during sleep. Therefore, in the light of Fulton's case, it seems justifiable to conclude that the relief which this patient obtained from headache by complete rest with the eyes closed was due to the freedom from strong visual stimuli and the consequent lessening in the volume of blood flowing through the visual cortex and, hence, through the tumor.

The epileptiform attacks, which were a prominent feature in this case during the four years prior to the first admission to the hospital, were of an unusual type. They were nonconvulsive and were characterized by an aura of numbness spreading from the distal portion of the upper extremities to the neck. This aura, which usually lasted about ten minutes before loss of consciousness occurred, was longer than is usual with epilepsy and was somewhat suggestive of a migrainous phenomenon. The loss of consciousness, however, readily distinguished the attacks from migraine. The bilateral character of the paresthesia in the aura indicated that a widespread disturbance in cortical function of the parietal lobes initiated the attacks. Evidence that the underlying process causing the seizures was progressing was obtained six months before death, when typical grand mal convulsive seizures appeared as well. Occurrence of the attacks was apparently determined by physical exertion, and their frequency or severity was not influenced by the administration of ordinary doses of phenobarbital. It is often observed that complete rest in the hospital lessens the frequency of attacks in cases of epilepsy, whether or not tumor is the basis of the condition. However, in this case the contrast between the complete freedom from attacks during three months in the hospital and the recurrence of frequent seizures on the resumption of a moderate régime of housework was striking. It was notable that the attacks always occurred during the day, and usually when the patient was engaged in some form of physical

9. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: The Cerebral Blood Flow During Sleep in Man, Brain **58**:44, 1935.

effort, as at the time of the seizure which led to her death. It appears that the increased circulatory rate associated with physical exercise acted as a stimulus to the occurrence of seizures in this patient.

In a review of the reports of cases of cerebral angiomas, one is impressed by the great frequency with which this tumor is associated with epilepsy. The attacks are often jacksonian in type, but generalized seizures are common. Weber [2a] reviewed 17 cases of meningeal hemangioma associated with nevi of the skin, in 13 (75 per cent) of which there were convulsions. Cushing and Bailey [1] remarked how regularly racemose angiomas, regardless of type, provoke epileptiform attacks. The probable explanation, they concluded, is that the middle cerebral artery, being the most widely distributed of the cerebral vessels, is most likely to be involved in an angiomatous malformation and that the paracentral convolutions, in consequence, are likely to be implicated. These authors cited 12 cases in which angiomas of either the venous or the aneurysmal type involved the cerebral hemisphere. In 8 of the cases there were convulsive seizures. Parker [10] found that major epilepsy occurred in about 21.6 per cent of 313 cases of verified cerebral tumor. The convulsions occurred more frequently, in the ratio of 5:1, with tumors situated in the frontal, parietal and temporal lobes, in that order of frequency, than with tumors elsewhere in the brain. Thus, the site of the lesion is an important factor in the predisposition to occurrence of epileptiform convulsions in cases of cerebral tumor. The fact that angiomas are primarily surface lesions may have a bearing on the greater incidence of seizures associated with these lesions than with tumors of other types situated in the same lobes of the brain.

However, a further explanation is suggested by the observations of Penfield [11] which indicate that marked vasomotor changes may occur in the cortex at the time of an epileptic seizure. He expressed the belief that these changes are the result of vasomotor reflexes subserved by autonomic neurons on the blood vessels of the brain and by a local vascular plexus which he concluded to be significantly increased in some cases. The exceptional frequency with which epilepsy is associated with supratentorial angiomas suggests the possibility that these lesions, by virtue of their vascular character, may predispose to a greater vasomotor instability of the cerebral blood vessels than do similarly situated tumors of other types. In the case recorded here there are certain features suggesting that the attacks were initiated by a vascular phenomenon of unusual sensitivity. The part played by physical exertion in precipitating the seizures and the ineffectiveness of drug therapy in controlling or modifying them were present in this case to a degree that is unusual in epilepsy. The character of the attacks also made it necessary to postulate widespread cerebral changes at the time of their occurrence. The lesion was situated at some distance from the rolandic region; yet attacks with a long bilateral sensory aura terminating in loss of consciousness, as well as generalized convulsive seizures, were described.

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10. Parker, H. L.: Epileptiform Convulsions, Arch. Neurol. & Psychiat. **23**:1032 (May) 1930.

11. Penfield, W.: The Evidence for a Cerebral Vascular Mechanism in Epilepsy, Ann. Int. Med. **7**:303, 1933.

Pathologic Features.—Most authors agree that angiomatous formations are not true neoplasms, but are in the nature of congenital anomalies. The facts supporting this view may be briefly summarized: 1. Glia fibers observed between the various vessels have been accepted as indicating an embryonic origin of the process.[1] 2. There is absence of formation of new vessels.[12] 3. The lesions do not behave like tumors —they do not form a solid, compact mass of proliferating cells, as is seen in benign or malignant neoplasms, but consist of an irregular conglomeration of vessels in which no cell has so increased in number as to dominate the others; they do not produce metastases locally or distally, and they do not displace brain tissue. All these conditions were fulfilled in our case.

The frequency with which angiomatous formations are observed in children may be considered as further evidence of their congenital origin. Certain authors [13] have pointed out that the embryonic development of the intracranial blood vessels makes it possible to explain the association of a varix of the dura, a nevus of the scalp or a venous angioma of the pia mater. Dandy,[13a] in considering the arterial type of angiomas, expressed the belief that maldevelopment of the original vascular bed would explain the nests of abnormal vessels which are interspersed between the arteries and the veins and which replace the normal capillary bed. He concluded that this communication may be one vessel or a group of vessels, but that no normal capillaries are present.

The slow development of symptoms that so often occurs in these cases is suggestive of cerebral tumor as the underlying lesion. It is also noteworthy that in certain cases symptoms do not develop until the second or third decade of life or later, and a few cases have been recorded in which no symptoms occurred, the condition being observed accidentally at autopsy. In an attempt to correlate these facts with a congenital origin, the pathologic condition must be considered in a little more detail. The venous angioma is composed entirely of veins and is presumed to arise from a peculiar deviation in the embryonic vascular channels. The lesion apparently grows in proportion to the rest of the tissues inside the skull, for no case has been described in which the cerebral tissue was distorted or displaced grossly by these lesions. The occurrence of symptoms is apparently dependent on the situation of the anomaly; it has been said [1] that the lesion produces symptoms early only if it involves the motor cortex. The walls of the veins forming these abnormal structures are thin and poorly developed, so that the vessels will readily dilate even under the modest venous pressure in the vessels of the brain. The dilatation probably occurs gradually, being proportional to the strength of the venous walls as well as to their tortuosity. This dilatation may produce disturbance in cortical function, which is manifested as epilepsy or hemiplegia if the lesion is situated over the motor cortex, although it never develops to the degree of producing gross cerebral distortion or actual increase in intracranial pressure.

12. Levine, V.: Angiomatous Malformations of the Brain: Report of Two Cases of Angioma Racemosum, Arch. Path. **15**:340 (March) 1933.

13. (*a*) Dandy, W. E.: Arteriovenous Aneurysm of the Brain, Arch. Surg. **17**:190 (Aug.) 1928. (*b*) Cushing and Bailey.[1]

On the average, arterial angiomas produce symptoms later in life than do venous angiomas. Dandy [13a] expressed the belief that these lesions may be divided into two types: first, those composed of both arteries and veins, and, second, those which are purely venous and later form arteriovenous connections, the veins subsequently becoming arterialized. In neither case is it likely that there is a direct flow of blood from arteries to veins in the early stages. The junction of the two systems is probably the result of trauma, as a number of cases have been reported [13] in which symptoms did not develop until a traumatic lesion of some type had occurred. The increased volume of blood rendered necessary by the presence of an arteriovenous aneurysm leads to dilatation of vessels even greater than that which occurs with the pure venous angiomas. In addition to the dilatation of the thin-walled and poorly formed veins which ordinarily takes place in these lesions, the condition may progress much more rapidly, owing to thrombosis of some of the vessels with, as a consequence, greater stress on those remaining patent. It is difficult to understand why the symptoms of the arterial angiomas should become manifest at a later period than those associated with the venous type. It may be possible that the vessels of the arterial angiomas are more resistant to pressure and that it is not until the arteriovenous communications become established that much dilatation occurs.

SUMMARY AND CONCLUSIONS

A case of cerebral angioma arteriale involving the inferior surface of the right temporal and occipital lobes is reported. The lesion was diagnosed during life and verified at autopsy.

Periodic right-sided headaches of a migrainous character were present for many years. The possible mechanism of their production is discussed, and, in view of the influence of strong or prolonged visual stimulation in their production, it is suggested that they were caused by increased blood flow through the lesion, associated with increased vascularity of the visual cortex, and the resultant effects on vessels in the portion of the meninges adherent to the tumor and to the base of the skull.

The high incidence of epilepsy in cases of cerebral angioma and the striking relationship between the seizures in this case and physical exertion are discussed. It is suggested that these lesions may predispose to greater vasomotor instability of the cerebral blood vessels than similarly situated tumors of other types.

The pathologic picture of cerebral angiomas is briefly considered, and certain aspects which have a bearing on the clinical syndrome are emphasized.

Prof. Duncan Graham gave permission for the publication of this case, and Prof. E. A. Linell assisted in the pathologic studies.

EXPERIMENTAL ANOXEMIA

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and
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A number of investigators, whose findings have been summarized by McFarland,[1] have reported changes in personality and mentality associated with anoxemia, and it is known that the extent of these changes depends not only on the severity of the anoxemia but on its duration. The experience of one of us (J. W. T.) during and after exposure to a low partial pressure of atmospheric oxygen for a considerable period is reported. The statements which appear in brackets, other than those recording time, were appended at a later date.

PROTOCOL OF EXPERIMENT

The experiment was carried out on Jan. 21, 1937. The subjects were Dr. D. B. Dill; Michele Gariepy, an artist; Zussman, a student; Harper, a student, and one of us (J. W. T.).

Notes During Exposure to Low Oxygen.—Started 10:17, cylinder evacuated by 10:24 [nitrogen cylinder]. Air analysis 9,000 feet after first cylinder. There may be a very slight confusion; this uncertain. Stopped emptying second cylinder 10:28—11,500. I feel this same sensation. There is no objective change in the behavior of those others present. Gariepy states 10:40 feels as though just had two glasses of beer—feels like reaching for his wallet to pay for it. Definite subjective change—slightly light headed; and if anything mind more confined to one thought; does not change as easily from one set of thoughts to another. More N. Not that I am concentrating better; it is as though other thoughts had been removed and I am dealing with the one remaining with the same amount of concentration as I would have given before but; Harper says he feels a bit fuzzy. Gariepy has yawning sensation. Gariepy sitting tracing the squares on his clothing with his finger; stopped when he noticed my observing him. Light to Michele seems a bit dimmer. 10:50—15,500. Michele says he feels as though he were in a hot bath in a close and warm room—feels rather silly, he says. Right upper eyelid has commenced a rapid tremor—more rapid than I have ever experienced—I have previously experienced this tremor when I am fatigued though never as rapid. My arm in writing feels tired and I feel like writing these notes any old way. [Writing at this point becomes less legible.] Zussman: 10:55 slightly dizzy—Harper 10:55 feels as though he were running on a full stomach slightly sick. He talks rather slowly and with little enthusiasm—feels sort of fuzzy "as though I had been drinking beer." Harper asked to introspect:—His interest in his experiment shows little emotional; More 11:00 N; shows dulling of affect.

1. McFarland, R. A.: The Psychological Effects of Oxygen Deprivation (Anoxemia) on Human Behavior, Arch. Psychol., 1932, no. 145.

Says his ideas seem more fixed. Zussman asked if he finds any difference in his thoughts—replies: "No, I haven't any." Personally feeling rather dizzy—Harper going through stereotyped motions—Michele belching and with slight headache. Harper says there is no diff. between this and alcohol. Michele—chest oppression "as though under a couple of feet of water." More N 11:6. My head and thoughts have cleared somewhat; Zussman: "dizziness slightly less." Harper: "Cheyne-Stokes." Zussman—looks cyanotic—Dill: "light consistently dimmer" I feel surprisingly well. Michele (11:12) feels that he can reason as well as before; feels that black color of ink more blue; My thoughts progressively improving in clarity. [Writing again normal.] Am aware that this may be due to lack of insight though convinced that it is not—Michele (11:14) severe frontal headache. Feel less like writing. (11:15). Zussman says "less inclined to giggle than before"; he is giggling more than before or so it seems to me. Michele lying down. Having hellish time spelling. 17,100—11:17. Dill concerned with Micheles condition—telling him to hyperventilate Michele amusingly lying on couch smiling, grimacing Michele; feels that his skin is somebody else's skin. Dill adjusting light to take M. Picture; some cards dropped; M. did not move; Dill lowered light and Michele drew up arms to protect face—as thought [though] light were falling. M: sees spots before his eyes. Does your mind feel clear to Harper—"Perfectly!" was emphatic answer Dill more talkative than I have ever seen him; in fact all. Michele says that his sense of humor more at liberty. Harper giggling to himself. Personally feel quite clear perhaps somewhat "heavy headed." No one as yet sugges [suggests] Schizo (11:42). More effort walking about. I have difficulty concentrating—Feels [feel] very muscularly weak. Feeling somewhat giddy—mentally stupid Tried taking blood from Dills artery without success—was clumsy in manipulations & did not get into artery. Blood ex Dill. Feeling giddy. Mentally very clear—[At this point blood was taken from my own artery, and others were asked to write notes as I dictated them.] Lay down at 12:30. Altitude 12:30 = 15,800 Altitude 12:45—17,000 Gariepy at 1:00 feels very sleepy—unwilling to do any more work than necessary Gariepy at 1:05 slightly dizzy 1:07 Michel—feels bad but disn't [doesn't] give a dam Zussman—dizziness slight—as in staying up late fidgety—Harper—O. K. concentrating a bit difficult. [Here I resumed taking notes.] Feeling somewhat giddy. 1:34—lunch—Personally feeling clear mentally—Actually excellent. [The writing here is scrawling and coming below the line on which it should be.] Michele tells me that a few minutes ago approx. 1:25 had uncontrollable bout of laughter. Everyone feeling particularly well after lunch; Pea soup and crackers 1:55 more N. 02. found higher. [There was a leakage into the chamber, which had been overlooked at the beginning of the experiment.] Dill 2:00 "Feeling a little giddy." Zussman difficulty in concentrating. Difficulty now—following story [told by Dill] 2:20 more N. More N. 2:15. 15,500 before last N feeling giddy and hellishly apathetic. 2:21 *sleepy* more (N) [I placed parentheses around the letter N for no apparent reason.] Feeling somewhat . . . [The writing is illegible.] Some . . . [The writing is illegible.] Lying arm; now, Some frontal headache and writing with slight tremor. 2:34 Harper, Michele feeling sick Dill seems unaffected Headache bad; splitting Headache parietal, frontal and around ears. 2:34 more N. Harper feeling ill; looks very pale cyanotic and breaking out into sweat. 120/78 at 2:46—Harper—nauseated feeling in stomach at 2:46—Zussman Feeling damned sleepy 2:50—16,500 Having head flat makes headache worse. 3:30 more N. Falling asleep suddenly jerked head over hand thinking my pencil in back of arm [I cannot recall what I meant by this sentence.] 3:10 I am indulging in a good deal of fantasy. 300 another short spasm [Here

again, I cannot recall what I referred to in this sentence.] 3:30 feeling intensely sleepy & apathetic as anything. Forcing myself to write these notes, would much . . . [writing illegible] sleep 3:40 stood up. I am absolutely apathetic would rather sit. Extremely difficult to follow dil Dills account of . . . [writing illegible]—may Can scarcerly [scarcely] read. 3:45 I feel terribly—[This was written immediately after normal oxygen had been restored.]

1. Dill
2. Schusman
3. Harper
4. Thompson
5. Michele

4:48—stopped

OBSERVATIONS

Physiologic data were obtained on three occasions on two of the subjects present in the chamber, with the results given in the accompanying table.

Postanoxic Period.—One of us (W. C.), who had not been exposed to the low oxygen tension, took charge of the other (J. W. T.) after the experiment had been terminated and recorded the following observations.

4:45 p. m.: On arrival at the chamber, Thompson was lying on the floor, leaning on his right elbow, head down, apparently not interested in the others. Dr. Dill was removing the cover from the ventilator. One person was sitting on a stool, slumped over, his arms hanging at his sides and a silly, inane expression on his face. Two others were present, one with his head under the hood of the camera.

4:48 p. m.: The door was opened. Thompson looked up at the clock, set down the time that the experiment ended (4:48 p. m.) and then slumped on the floor, apparently collapsed; his eyes were closed; his face was somewhat pale. The conversation of the others in the room was concerned with their subjective reactions to the lights. The atmosphere was close and stuffy, but otherwise not unusual. I helped Thompson up; he appeared weak and held his hands to his eyes and forehead. He complained of headache after leaving the chamber, at 4:50 p. m.

4:50 p. m.: Thompson was sitting in a chair in the laboratory; he appeared tired and responded to questions in monosyllables. He was holding his hands to his forehead and complaining of severe headache. He refused aminopyrine. He had some difficulty in walking upstairs, stumbling and staggering slightly, and collapsed onto the back seat of the car.

4:55 p. m.: While waiting for the traffic light to change on the Larz Anderson Bridge, he became nauseated. He said: "You'd better stop; I'm going to be sick." Before the car could be maneuvered to the side of the road, Thompson opened the door and walked hurriedly over to the embankment, near the river. He vomited several times, the last with some force. He was assisted back to the car, still holding his hands to his head and appearing weak. There was no conversation during the rest of the trip back to the hospital.

5:20 p. m.: On arrival at the hospital, Thompson was sitting back, with his head in his hands; he paid no attention to requests to come out. Eventually he was persuaded to leave the car and walked into the apartment. He appeared weak and dazed, looked about him in an uncomprehending manner and collapsed on the bed. The heart rate was 40 and regular; the sounds were of good quality.

Physiologic Data on Two Subjects Subjected to Experimental Anoxemia

	Carbon Dioxide Tension of Alveolar Air, %		Oxygen Tension of Alveolar Air, %		Arterial Carbon Dioxide, Cc. per 100 Cc. Blood		Arterial Oxygen, Cc. per 100 Cc. Blood		Saturation Arterial Blood, %		*pH*		Cell Volume		Respiratory Rate		Pulse Rate		Blood Pressure, Mm. of Mercury	
	D.B.D.	J.W.T.	D.B.D.	J.W.T.	D.B.D.	J.W.T.	D.B.D.	J.W.T.	D.B.D.	J.W.T.	D.B.D.	J.W.T.	D.B.D.	J.W.T.	D.B.D.	J.W.T.	D.B.D.	J.W.T.	D.B.D.	J.W.T.
Time	9:41	9:20	9:41	9:20	9:41	9:20	9:41	9:20	9:41	9:20	9:41	9:20	9:41	9:20	9:41	9:20	9:41	9:20	9:41	9:20
	39.3	41.8	106.6	95.7	47.60	51	....	....	....	....	7.395	7.416	....	44.3	14	15	61	62	112/74	110/64
Time	10:45	12:47	10:45	12:48	10:45	12:48	10:45	12:48	10:45	12:48	10:45	12:48	10:45	10:49	10:45	12:48	10:45	12:48	10:45	12:48
	29.9	36.8	47.3	35.3	47.39	51.29	....	....	62.4	42	7.440	7.423	....	42.6	28	18	82	70	128/80	108/78
Time	3:46	3:30	3:46	3:30	3:40	3:30	3:46	3:30	3:46	3:30	3:46	3:30	3:46	3:30	3:46	3:30	3:46	3:30	3:46	3:30
	33.2	36.9	40.7	33.3	47.43	49.97	....	....	59	52.9	7.46	7.454	....	45	15	16	98	78	....	110/80

The pulse was shallow. Respirations were regular and shallow, at times almost imperceptible. He was undressed with difficulty. He was entirely unresponsive to questions and other stimuli. Artificial respiration was given. He did not reply to questions but nodded his head to indicate that he was tired. He did not know where he was or who the examiner was. The impression was that of a person just coming out of anesthesia. Deep breathing and artificial respiration were carried out every five minutes. The pulse was still slow, the rate varying from 40 to 52, the latter after deep breathing and artificial respiration. Cold applications were made to the forehead and chest. Questioning repeated at frequent intervals elicited no vocal response. He cried several times when asked his name and where he was. Acetylsalicylic acid, 10 grains (0.65 Gm.), was given. He attempted to pour water from a glass on his chest.

6:30 p. m.: A cool bath was given for several minutes, followed by exercises consisting of bending over and touching the hands to the floor fifteen times, with subsequent deep breathing. He still did not know where he was or his or the examiner's name. He acquiesced readily in obeying orders. The facial expression was blank. When questioned, he stared at the examiner; his eyes wandered about; he appeared to be trying to orient himself. This inspection of surroundings had been noticed for the past half hour. Another cool bath was given.

6:45 p. m.: He whispered his own name, as well as the examiner's. He stated that he was tired and sleepy. Deep breathing and exercises were carried out. The heart rate was 60 and the pulse was stronger. Respirations were still shallow.

7 p. m.: He was out of bed and exercised, with deep breathing. He appeared slightly more responsive, but the reactions were still sluggish. He was barely able to move his feet up and down. He still did not reply to questions, except to reiterate names. He did not know where he was; he was told the name and exact location of the hospital.

7:30 p. m.: He was more responsive, but appeared apathetic and indifferent. He was suggestible, agreeing to anything. He stated he was unable to think or concentrate. There was no headache or other subjective symptoms and no emotional state—either happy or sad. He remembered the name of the hospital and where he was, which had been told him previously. He was not much interested in what became of his notes. He said that today was Thursday and that he was in the chamber yesterday. Answers to questions consisted of nods or shakes of the head.

7:45 p. m.: He was not sleeping. Responses were somewhat quicker. He denied having subjective symptoms. Deep breathing and exercises were carried out. He was not hungry. He recognized where he was and insisted that today was Thursday and that he was in the chamber. He said that today's date was January 20. When asked to introspect regarding his present state, he said he was "all right." He did not want to do anything and was willing to lie down. He appeared more interested in his immediate surroundings, straightened the rug with his feet and looked about the room. He insisted on asking for his notes, but beyond this showed no interest in them. He stated that the last notation he made was "7800." The facial expression was unchanged; it was one of complete blankness and was devoid of feeling or indication of animation or intelligence. The replies were automatic.

8-8:10 p. m.: He was awake and lying in bed. He stated that he was "all right." Exercises and deep breathing were performed. He remembered his name and the place and replied to other orienting questions previously answered

correctly. He remembered that Dr. Dill was in the chamber with him. There were three others, but he did not remember their names. When Zussman was mentioned, he recalled that he was there. He stated that "Michelson" was not there, that he left the chamber at 6:30 p. m. and that he was there yesterday (Wednesday). When this was questioned, he stated that maybe it was today; he was not sure. He did not know why he was being asked to breathe deeply. He insisted that there was nothing the matter with him, that he felt all right. He apparently had no insight. The facial expression was unchanged. The general attitude was one of listlessness, inattention and apathy. He went to the bath room.

8:30 p. m.: No change was evident. He still complained of being tired. There was no insight. Behavior was not spontaneous. He recalled that the date was January 21. He knew that he had been in the chamber. Deep breathing and exercises were performed.

9 p. m.: He took tea and toast. He was still tired, but not sleepy. There were no symptoms and no insight. The heart rate was 60. Deep breathing and exercises were performed.

9:15 p. m.: There was more spontaneity. He asked how the others were when they left the chamber and when he left it. He was still listless and tired and preferred to be left alone.

9:45 p. m.: He awakened easily. He stated he felt all right, inquired as to what happened after leaving the chamber and asked for a cigaret. He stated that he was feeling strange, in a way he had never felt before. It was difficult to describe this feeling. The first thing that struck him was that objects were extraordinarily clearcut. At the same time, he felt completely worn out, both physically and mentally. His mind was not confused, nor was it very clear; it seemed functionless, more "like perceptions and nothing else." There seemed to be no interpretation of these perceptions and no thoughts. There was nothing to concentrate on. He realized that he had never felt this way before. He was not frightened, and the state was neither pleasant nor unpleasant. There appeared to be no emotional feeling. He realized that there were things about which he should be concerned, such as what happened in the chamber, but he was not. If his notes were destroyed he knew he should feel concern, but he did not. Intellectually, he realized all these things, but he could not become enthusiastic. He was content merely to lie in bed. He was neither happy nor sad, just devoid of all feeling. He felt conscious of his body—that his body existed but that his mind did not. He recalled the most terrific headache he ever experienced in his life. He was sure that this headache was different from that which any one had ever had. He could not imagine any one having a similar headache and still living. He did not know that such pain existed. The nearest thing he could think of with which to compare the headache was for some one to pull his skull apart. He did not have this degree of headache in the chamber and did not suffer at all until he left it. After he came out he opened his eyes once, but had to close them because the pain was intensified. He felt all right in the chamber until near the end of the experiment, when he became sleepy and felt faint and slightly sick. He was aware of the others, but did not care about them. He did not recall recording the time that the experiment ended. He remembered thinking that he should be making notes, but could not do this. He appeared to be in a state of complete lassitude and indifference. He recalled when Dr. Dill opened the ventilator, but it meant nothing to him except that he felt slightly annoyed because the lid was taken off; it seemed like such a futile thing to do. At present, he was much aware of noises, but they did not bother him. He realized that he

was not himself, but did not care. Objectively, there did not appear to be any marked change in facial expression. There was more animation, but he did not smile or exhibit any emotional state. Replies were spontaneous, not irrelevant or wandering.

10:30 p. m.: He had been sleeping, but awakened easily. There was no change since the previous note was recorded. He wanted only to sleep. Deep breathing was carried out for several minutes.

11:15 p. m.: He had been sleeping, but awakened readily when touched. He stated that he felt fine and smiled slightly. He was induced to breathe deeply. He appeared slightly restless. The pulse was regular and more rapid; the rate was approximately 70 and the quality good. The color was good.

January 22: 1 a. m.: He had been asleep and felt fine. Deep breathing was performed at this time.

3 a. m.: He had been asleep, but was awakened easily. He stated that he felt better. He believed that his emotional tone was better than before. He was still tired and sleepy.

7 a. m.: He awakened from sleep easily. He said he was much better, although he still felt strange. There was some emotional feeling. He was still tired and sleepy. Deep breathing was carried out.

9 a. m.: He awakened readily. Breakfast consisted of tea and toast. He requested that the observation that his mouth was parched and dry be entered in the notes. He still felt somewhat apathetic and listless and did not want to do anything. He continued to appear expressionless and dull.

9:45 a. m.: He was urged to get out of bed. Exercise and deep breathing were carried out. When asked what he wanted to do, he replied that he would shave and then look over his notes.

10 a. m.: He shaved and took two cold baths. He stated that he felt better after the second bath. He dressed and walked to the automobile. There was some incoordination; when asked how he felt, he replied that it seemed as if his legs were moving by themselves, a queer sensation; the motion did not appear spontaneous. He stated that he felt all right, but continued to look uninterested and offered little spontaneous conversation. On return from the drive, his legs still felt queer and seemed to move by themselves in a peculiar flail-like action. He rested in the apartment during the morning and examined his notes. He walked up to dinner. The legs still felt incoordinated. Mental functions were more alert. Objectively, he appeared improved.

Note in Afternoon: He appeared much improved, almost normal. He was still tired, and it was the impression of the examiner that he had not yet fully recovered his faculties. He stated that subjectively he was much better.

COMMENT

Throughout this stuporous or semiconscious postanoxic period perception was not seriously impaired. The environmental phenomena were registered much as they might have been on a photographic plate, receiving only the slightest degree of personal interpretation. Conative functions were absent, except as one experienced a vague and indistinct desire to be left undisturbed. However, this wish was never sufficiently clear to result in any purposeful action which might have achieved its gratification. Similarly, affect was totally in abeyance. At one stage, when the respiratory system had almost completely failed and artificial respiration was being administered, one experienced no concern whatever, in spite of being aware of these occurrences. Questions frequently

evoked some answer, which occasionally was given expression. The answers appeared in one's mind and were stated rather in the fashion of a knee jerk; i. e., volition played an insignificant role, or, to put it in another way, it seemed that the answers were formulated rather than that the subject formulated them.

Motor responses were slow, and this, with the diminution in volition, may have been the result of a feeling of extreme exhaustion. Any activity required the greatest amount of effort, not only for its execution but even more for its initiation. The behavior may at times have suggested normal activity, but on such occasions an observer would have been unaware of the tremendous effort being expended in order to perform a relatively simple task. Motor difficulty characterized by incoordination and spasticity of the lower limbs appeared soon after the anoxemia had been terminated and persisted with diminishing intensity until the following day. There were no delusional or hallucinatory experiences, although it is of interest to note that one subject has been observed who has active visual hallucinations after breathing a mixture low in oxygen. This subject is being studied by Dr. George Wald, who will give a more complete report at a later date.

It is difficult to state when the symptoms thus produced totally disappear. Certainly, in the case reported here it was several days at least before the subject felt entirely recovered, and, judging by the mistakes which were made in routine laboratory work for a week or more subsequent to the anoxic period, it is likely that residual impairment was prolonged. It is a curious fact that both the mental and the physical aberrations in cases of anoxemia have been more severe after the anoxemia, a feature to which Haldane has called attention and which we have observed also in dogs subjected to a low partial pressure of oxygen.

SUMMARY

A case of experimental anoxemia which resulted in severe physical and mental manifestations is reported.

SMALL ANEURYSM COMPLETELY OBSTRUCTING LOWER END OF AQUEDUCT OF SYLVIUS

G. F. Rowbotham, F.R.C.S., Manchester, England

The present communication is concerned with a case of intermittent hydrocephalus caused by a saccular aneurysm which formed on one of the vessels in the roof of the aqueduct of Sylvius.

REPORT OF CASE

History.—On Oct. 14, 1936, a girl aged 11 was admitted from Hull, England, to the neurosurgical unit of the Manchester Royal Infirmary, under the care of Mr. Geoffrey Jefferson, complaining of headaches, blurred vision and attacks of unconsciousness.

The parents stated that up to the age of 6 years the patient had been healthy. She then had a severe attack of scarlet fever, after which certain mental changes took place. Previously of a bright, happy disposition, she became slow and irritable. From this time, gradual deterioration in vision had been observed. On July 28, 1936, she came home from school at midday complaining of headache; she insisted on returning in the afternoon, as it was the last day of the term, but after 4 o'clock the headache became worse and she was put to bed. Two hours later she was found unconscious on the bedroom floor. She made a rapid recovery and was able to return to school, though from this time she suffered from recurrent attacks of severe headache, which usually came on in the morning, starting in the nape of the neck and shooting forward over the vertex into the frontal region. The headaches were in the nature of spasmodic pains, lasting for a few minutes and then disappearing.

Clinical Observations.—The child was kept under observation for a few days; at times she was very sleepy and difficult to rouse. This stupor did not resemble a cerebellar fit, as there was no opisthotonos or evidence of medullary embarrassment. In the more lucid intervals, indefinite signs of cerebellar involvement in the arms and legs were discovered; the child was inattentive, and the widely dilated pupils reacted sluggishly to light. The optic nerve heads were edematous, but the lazy reactions of the pupils to light could not be accounted for by secondary atrophic changes; the possibility of a tumor of the quadrigeminal plate was therefore considered. It was decided that ventriculographic examination was necessary. On the morning planned for the operation the child's condition became much worse; she was stuporous; breathing was shallow, and the pulse was thin and rapid. The pupils were fixed, and there was a slight droop of the upper eyelids.

Operation.—Because of the grave change in the child's condition, it was deemed inadvisable to carry out any detailed studies with air replacement; in the hope, therefore, that there might be a tumor high in the vermis with an extension

compressing the midbrain, a rapid cerebellar exposure was made, but no tumor was observed. The tonsils were not herniated, and a good view was obtained into the fourth ventricle. An attempt to pass a fine catheter into the iter failed, an obstruction proving impassable to gentle pressure.

The child died on the next day.

Postmortem Observations.—The gyri were flattened and the sulci small—the cortical pattern associated with a general rise in intracranial pressure. A sagittal section in the midline showed an interesting picture. The aqueduct of Sylvius, the third ventricle and the lateral ventricles were all considerably dilated. Filling completely the lumen of the aqueduct, at its lower end, just above the entrance into the fourth ventricle, was a round, dark bluish red mass, the size of a small pea.

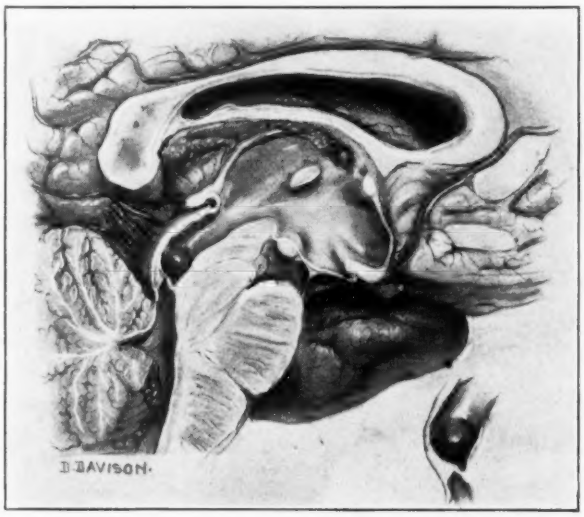


Fig. 1.—Drawing of a small aneurysmal sac obstructing the iter of Sylvius.

Immediately below the tumor was a shelf jutting from the wall of the aqueduct, in the middle of which was a small perforation, the only communicating pathway between the aqueduct and the fourth ventricle (fig. 1). It could be easily appreciated how this complicated structure of the round tumor and shelf could form a ball valve obstruction to the passage of the cerebrospinal fluid and so account for the length and periodicity of the symptoms.

The swelling was shown by histologic study to have the typical structure of a thrombosed blood vessel and was probably an aneurysm of the saccular type (fig. 2). A vein was seen in close proximity, but no communication was observed between the two to suggest an arteriovenous aneurysm. It may be suggested, as the symptoms followed an attack of scarlet fever, that the aneurysm was of the mycotic type, resulting from weakening of the arterial wall by inflammatory embolic softening. The outer coat was composed of several layers of fibrous tissue, with concentric fibrofibrinous laminations attached to its inner surface, encroaching on the central cavity. Blood cells filled the central cavity and were enmeshed between the fibrinous laminations and the fibrous layers of the outer coat. Probably the aneurysm developed in one of the perforating branches of

the superior cerebellar artery, as shown by the roentgenogram of a specimen into which an injection of bismuth in gelatin was made by Mr. J. Hardman to show the blood supply of the roof of the aqueduct to which the aneurysm was attached (fig. 3).

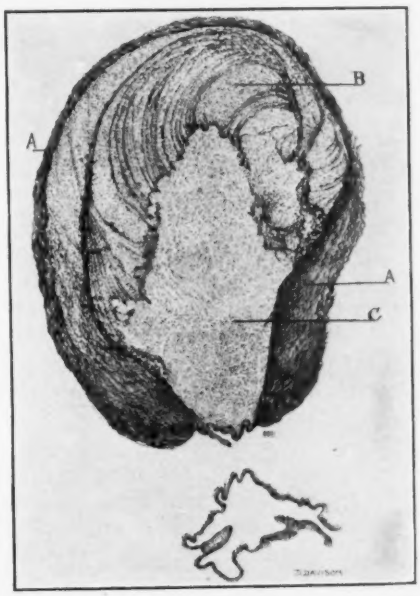


Fig. 2.—Drawing of a photomicrograph of the aneurysm, showing (*A*) the fibrous wall, (*B*) the laminated fibrosing clot and (*C*) erythrocytes.

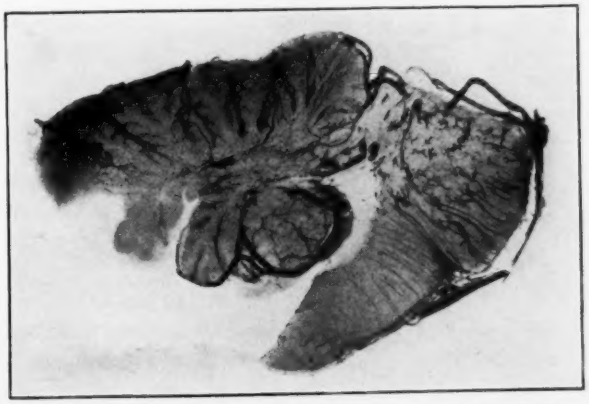


Fig. 3.—Injection of bismuth in gelatin (Mr. J. Hardman), showing the superior cerebellar artery as the most probable vessel of origin.

This case is reported because I believe that it is the first case to be described of an aneurysm growing from a blood vessel in the roof of the sylvian aqueduct and obstructing its lumen.

Technical and Occasional Notes

ABSENCE OF THE SEPTUM PELLUCIDUM AS THE ONLY ANOMALY IN THE BRAIN

Report of a Case

VERA B. DOLGOPOL, M.D., NEW YORK

Absence of the septum pellucidum is known chiefly as an anomaly complicating complete or partial aplasia of the corpus callosum; malformation of the fornix is also often present in such cases. Absence of the septum pellucidum with all other structures of the brain properly developed, however, is rare. Only 4 cases of this anomaly in fully developed brains and 2 cases in fetal brains have been reported.

The first case was reported by Tenchini [1] in 1880. The brain was that of a boy aged 2½ years who died of tuberculous meningitis on the fifth day of illness. The septum pellucidum was absent, and the fornix was not adherent to the lower surface of the corpus callosum. The soft commissure was absent. The child was normal mentally.

The next case was described in 1925 by Hochstetter.[2] The brain was observed in the dissecting room. There was no hydrocephalus. No history of the case was available. Prior to this case, Hochstetter saw absence of the septum pellucidum in otherwise well formed brains of fetuses 118 and 168 mm. in crown-rump length (about the third and fifth month of gestation respectively); 1 of the brains showed internal hydrocephalus. Hochstetter expressed the belief that congenital absence of the septum pellucidum is not rare and that it usually escapes attention.

Hahn and Kuhlenbeck,[3] in 1930, also encountered this anomaly in the dissecting room; no information on the history of the patient could be obtained.

In 1935 Dyke and Davidoff [4] observed the absence of the septum pellucidum in encephalograms of a woman aged 23 with postencephalitic disorders of behavior.

From the Pathologic Laboratories of the Central and Neurological Hospital, Welfare Island.

1. Tenchini, L.: Un caso di assenza completa del setto lucido in un bambino di anni due e mezzo colla integrita delle funzioni intelletuali, Boll. scient. **2**:65, 1880.

2. Hochstetter, F.: Ueber Fälle vom vollstandigen Fehlen der Septum pellucidum beim Menschen, Sitzungsb. d. k. Akad. d. Wissensch. Math.-naturw. Cl. (Abt. 1; supp.) **134**:1, 1925.

3. Hahn, O., and Kuhlenbeck, H.: Defektbildung des Septum pellucidum im Enzephalogramm, Fortschr. a. d. Geb. d. Röntgenstrahlen **41**:737, 1930.

4. Dyke, C. G., and Davidoff, L. M.: Congenital Absence of the Septum Pellucidum, Am. J. Roentgenol. **34**:573, 1935.

As no hydrocephalus was present in any of these cases, the anomaly was considered to be congenital.

Absence of the septum pellucidum was observed at autopsy at the Central and Neurological Hospital in a patient from the medical service of Dr. P. Clinton Pumyea, who permitted me to report the case.

REPORT OF CASE

Clinical History.—A white woman aged 60, a domestic, single, entered the hospital with complaints of weakness and loss of weight. She was emaciated and weak, but mentally alert.

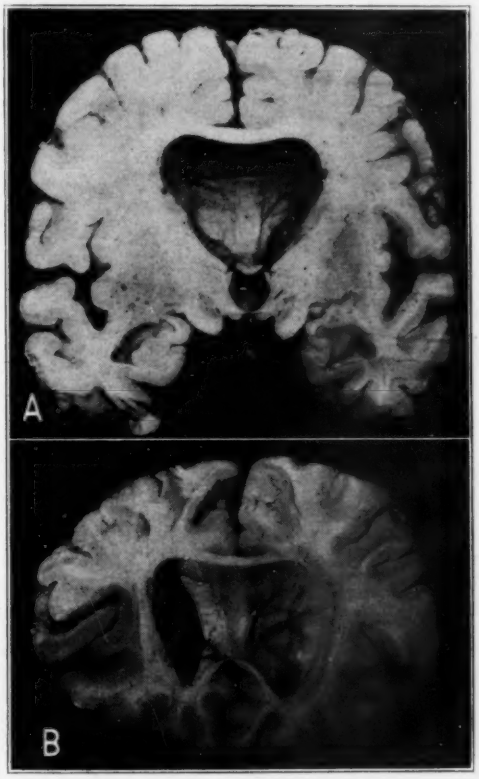


Fig. 1.—Photographs looking forward, showing absence of the septum pellucidum.

Neurologic examination, made in the course of the physical examination, revealed nothing abnormal; no special investigation of the patient's mentality was undertaken. There were dilatation of the aorta, a blood pressure of 180 systolic and 90 diastolic and enteroptosis. The Wassermann and Kahn reactions of the blood were negative.

After three weeks in the hospital extrasystoles developed. A few days later there was simultaneous occlusion of the left axillary and the left femoral artery, and the patient died within twenty-four hours.

Autopsy.—As this could be performed only after five days, the brain was fixed in situ by injection into the cisterna magna of an 8 per cent solution of formaldehyde U. S. P. The observations were: atheromatosis of the coronary arteries; atheromatosis of the aorta, with a mural thrombus in the lumbar region; thrombosis of the left subclavian and axillary arteries, and incipient bronchopneumonia. The peripheral arteries of the lower extremities could not be dissected.

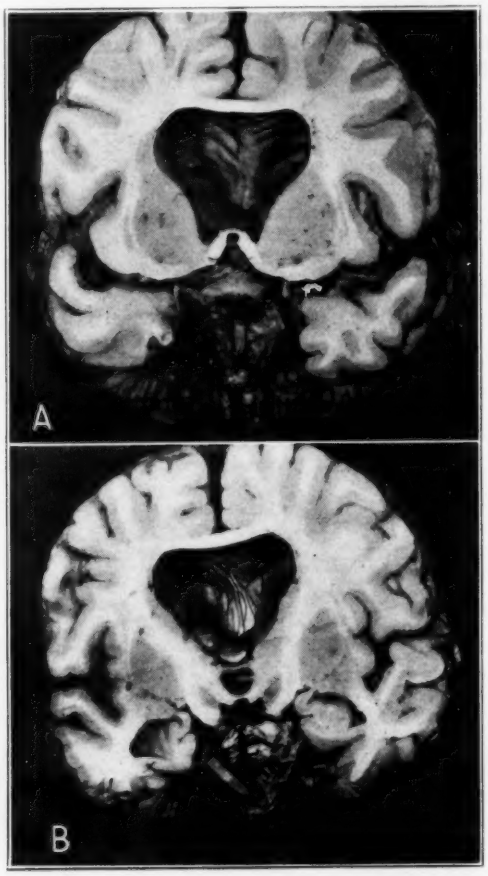


Fig. 2.—Photographs looking backward, showing absence of the septum pellucidum.

The brain showed marked atrophy of the cortex, with widening of the sulci. The cortical and the internal carotid arteries were of normal diameter, moderately sclerosed and gaping, while the basilar artery was not sclerotic.

The brain was fairly well fixed. A section through the frontal lobes revealed a single ventricle anteriorly, without a septum pellucidum (fig. 1 *A*). The brain was then placed in a 4 per cent solution of formaldehyde U. S. P. to complete fixation. Further sectioning of the brain after fixation showed the presence of two faint ridges, on the anterior wall of the anterior ventricular space, about 1 cm. apart on either side of the midline (fig. 1 *B*), apparently indicating the lines along which the septum pellucidum, with its wide cavum, had previously

been attached. The lining of the ventricle over the ridges was smooth and shiny. Moderate internal hydrocephalus was present, as evidenced by rounding of the angles between the corpus callosum and the heads of the caudate nuclei and by widening of the subthalamic part of the third ventricle. The white matter of the hemispheres and the corpus callosum were atrophic. The fornix was not adherent to the corpus callosum, except at the lowermost part of the splenium, and rested on the massa intermedia (fig. 2 *B*). The large single anterior hemispheral cavity divided posteriorly into paired posterior and inferior horns; it was connected with the third ventricle by means of normal foramens of Monro (fig. 2 *A*). The roof of the single cavity was formed by the corpus callosum. The blood vessels from the lower surface of the corpus callosum in its posterior part left the roof near the midline and ran unsupported through the cavity to the posterior columns of the fornix (fig. 2 *B*); these loose parts of the blood vessels, however, were obliterated. The anterior and posterior commissures were present. The aqueduct was patent, and no obstruction was present in the region of the fourth ventricle.

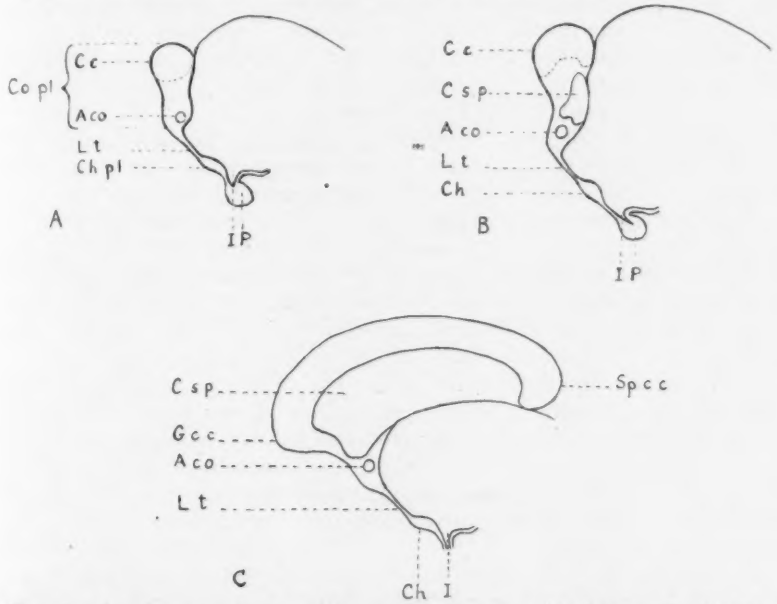


Fig. 3.—Development of the septum pellucidum (modified from Hochstetter [5]). *Co pl* indicates the commissural plate; *C c*, the corpus callosum; *G c c*, the genu corporis callosi, *Sp c c*, the splenium corporis callosi; *C s p*, the cavum septi pellucidi, *A co*, the anterior commissure; *L t*, the lamina terminalis; *Ch pl*, the chiasmal plate; *Ch*, the chiasm; *I*, the infundibulum, and *P*, the pituitary gland.

COMMENT

The case appears to be one not of aplasia but of secondary disappearance of the septum pellucidum. The questions requiring clarification are (*a*) whether the septum pellucidum was of normal configuration at the time of disappearance; (*b*) whether it disappeared, as a whole or in part, in the fetal or in the postnatal period, and (*c*) whether the internal hydrocephalus was instrumental in the disappearance of the septum pellucidum.

In regard to the shape and size of the septum pellucidum, one may assume that the normal shrinkage of the posterior part of the septum pellucidum never took place, as the fornix was not adherent to the lower surface of the corpus callosum. The extreme length of the obliterated loose blood vessels connecting the corpus callosum and the posterior columns of the fornix, even if due in part to the hydrocephalus, supports this assumption.

Hochstetter [5] explained congenital absence of the septum pellucidum on the basis of his investigations on the formation of the septum pellucidum and of its cavum. He dissented from the opinion of embryologists who held that the cavum of the septum pellucidum is part of the median fissure, separated by adhesion of the median surfaces of the hemispheres along a line of closure reenforced by the rostrum of the corpus callosum. He observed that the cavum of the septum pellucidum forms within the "commissural plate" (which is a thickened upper part of the lamina terminalis), between the corpus callosum and the anterior commissure, through resorptive processes leading to the formation of fluid-filled spaces with fibers running through them; later, the loose fibers become incorporated into the wall, and the smooth-walled cavum of the septum pellucidum results (fig. 3). In the opinion of Hochstetter,[2] the process of resorption may occasionally involve the walls of the cavity to a greater extent than normal, resulting in disappearance of the walls, i. e., of the septum pellucidum.

Whether the process of disappearance of the septum pellucidum took place in the prenatal or in the postnatal life of this patient, it occurred long before death, judging from the smooth, continuous surface of the single ventricle, without remnants of the septum pellucidum. The length of the obliterated vessels in the posterior part of the cerebral cavity suggests that the posterior part of the septum pellucidum could have persisted for a time in postnatal life. The obliteration of these vessels could also have played a part in resorption of the septum pellucidum by impairing the nutrition of that structure; however, there was no way of establishing the age of occlusion of these vessels.

The internal hydrocephalus in this case was obviously of compensatory character, developing as the result of arteriosclerosis with atrophy of the white substance.

If the septum pellucidum was present in part at the time that the hydrocephalus developed, the latter probably contributed to the atrophy and disappearance of the remnants of the septum pellucidum, as it not infrequently contributes to the fenestration of that structure.

5. Hochstetter, F.: Beiträge zur Entwicklungsgeschichte des menschlichen Gehirns, Vienna, Franz Deuticke, 1919, pt. 1, pp. 109-140.

Abstracts from Current Literature

Anatomy and Embryology

AN ANENCEPHALIC HUMAN EMBRYO 16.5 MM. LONG. G. S. DODDS and EUGENE DEANGELIS, Anat. Rec. **67**:499 (March 25) 1937.

Dodds and DeAngelis describe briefly a moderately well preserved anencephalic embryo. The crown-rump length was 16.5 mm., and the body resembled that of an embryo of about 7 weeks. The brain consisted of a thin sheet of primitive nerve tissue, giving rise to several pairs of cranial nerves. RIOCH, Boston.

HEREDITARY DEFECTS OF THE CORPUS CALLOSUM IN THE MOUSE, MUS MUSCULUS. LESTER S. KING, J. Comp. Neurol. **64**:337 (Aug.) 1936.

Twenty-three series of abnormal brains of mice cut in various planes were stained with the Weigert or the Cajal silver method or with thionin. Normal brains were also available for comparison. The brains exhibited defects of the corpus callosum and presence of the longitudinal bundle. Abnormalities consisted of (1) complete absence of the corpus callosum, (2) presence of a partial but atypical commissure only anteriorly, or (3) presence of the commissure only posteriorly. In the first type the longitudinal bundle gave rise to no commissural fibers. The fornix longus, angular bundle, indusium and stria Lancisi took a course quite different from the normal. In the second type the longitudinal bundle gave rise to a band of commissural fibers over the psalterium. In the third type the longitudinal bundle was present, but commissural fibers arose from its posterior half to form a well defined splenium, similar in many respects to the normal. Three mice showed defects of type 3. The longitudinal bundle is thought to be composed of fibers from the cells of origin of the corpus callosum. Hindered by some genetic factor, these fibers run in a well defined course in the ipsilateral hemisphere. In all types the cytoarchitecture of the cortex was normal. Mice showing these various types of abnormalities do not breed absolutely true. Litters from two defective parents may occasionally include normal mice, or the abnormality may differ from that possessed by the parent. Nevertheless, King believes that the longitudinal bundle is a definite hereditary feature, which forms a new mutation of Mus musculus. ADDISON, Philadelphia.

THE EFFERENT FIBERS OF THE EDINGER-WESTPHAL NUCLEUS. RICHARD L. CROUCH, J. Comp. Neurol. **64**:365 (Oct.) 1936.

In the experiments performed by Crouch, the Edinger-Westphal nucleus of the cat was studied for chromatolysis after (1) removal of the ciliary ganglion, (2) enucleation of the eyeball and (3) cutting the oculomotor nerve intracranially. The results were negative after removal of the ciliary ganglion; however, since only the ends of the axons were affected, the degeneration may not have reached back as far as the nucleus. In the enucleation of the eyeball the oculomotor nerve was cut nearer the brain, and presumably nearer the cell bodies. Most of the cells of the Edinger-Westphal nucleus on the same side were in some stage of degeneration. There was some degree of chromatolysis in the contralateral Edinger-Westphal nucleus. In the third series of experiments the oculomotor nerves were cut intracranially. Chromatolysis was a little more definite than in the preceding experiments. Crouch's observations support the theory that the Edinger-Westphal nucleus controls pupillary constriction and sends both crossed and uncrossed fibers to the nerve. FRASER, Philadelphia.

MYELINATION IN THE CENTRAL NERVOUS SYSTEM OF THE ALBINO RAT, TREATED WITH THYMUS EXTRACT (HANSON). ALBERT C. BUCKLEY, J. Comp. Neurol. **66**:449 (April) 1937.

The investigations in Rowntree's laboratory on the biologic effect of thymus extract in accelerating growth and development in the albino rat suggested this study of the development of myelin in the central nervous system of rats treated. Rats were treated with thymus extract for a number of generations. The normal rat has no myelin until forty-eight hours after birth. When 6 days old it has fairly definite myelination in the cervical region of the spinal cord. The 6 day rat of the sixth generation treated with thymus extract showed myelination in the spinal cord equivalent to that of the normal 13 day animal; the 6 day animal of the tenth generation treated with thymus extract showed myelination equivalent to that of the rat 20 days of age.

ADDISON, Philadelphia.

QUANTITATIVE STUDIES OF THE VAGUS NERVE IN THE CAT: I. THE RATIO OF SENSORY TO MOTOR FIBERS. JAMES O. FOLEY and FRANKLIN S. DUBOIS, J. Comp. Neurol. **67**:49 (June) 1937.

The purpose of this study was to count the number of sensory and motor fibers in the vagus nerve of the cat. The right and left vagus nerves were studied in 2 normal cats and in 9 others in which the efferent fibers of the right vagus nerve had been eliminated by intracranial section of the vagoaccessory roots twenty days previously. After suitable preparation, the cells in the nodose ganglion and the fibers proximal and distal to it were counted. Only from 20 to 35 per cent of the total number of fibers in the vagus nerve were eliminated by intracranial section; from 33,555 to 39,166 axons were enumerated in the normal vagus nerve. Only from 23 to 33 per cent were myelinated, and of these from 36 to 46 per cent were sensory. The number of fibers in the vagus nerves of the two sides were normally approximately equal. Foley and DuBois conclude that the vagus nerve of the cat is predominantly sensory and predominantly unmyelinated.

QUANTITATIVE STUDIES OF THE VAGUS NERVE IN THE CAT: II. THE RATIO OF JUGULAR TO NODOSE FIBERS. FRANKLIN S. DUBOIS and JAMES O. FOLEY, J. Comp. Neurol. **67**:69 (June) 1937.

All operations were performed on the right side in adult cats. In 6 animals the vagoaccessory roots were sectioned at their points of emergence from the brain, and from five to eleven days later the nodose ganglion was removed. After two weeks the pharyngeal and auricular nerves, the jugular ganglion and the trunk of the vagus nerve distal to the ganglion were suitably prepared for counting the fibers and cells. Sixteen cats were subjected to one of the following four procedures: (1) section of the vagus nerve proximal to the origin of the pharyngeal nerve; (2) section of the auricular nerve; (3) ligation of the external carotid artery and removal of the tympanic bulla, and (4) ligation of the external carotid artery and removal of the bulla and the thin plate of bone covering the auricular nerve. In only 1 cat were suitable counts obtained in all places—8,451 cells in the jugular ganglion, 6,237 fibers in the auricular nerve and 1,298 fibers in the vagus nerve distal to the ganglion; 1,990 fibers in the auricular nerve and 762 fibers in the vagus nerve were myelinated. Few cells of the jugular ganglion underwent frank chromatolysis after section of the vagus nerve, but a large number showed retrograde change after section of the auricular nerve. The results indicate that relatively few sensory fibers in the cervical portion of the trunk of the vagus nerve arise from cells in the jugular ganglion.

ADDISON, Philadelphia.

DEVELOPMENT OF SPINAL REFLEX MECHANISM IN HUMAN EMBRYOS. W. F. WINDLE and J. E. FITZGERALD, J. Comp. Neurol. **67**:493 (Oct.) 1937.

In studying the development of the spinal cord of human embryos, Windle and Fitzgerald examined 14 embryos between 5 and 8 weeks old prepared by the pyridine-silver method. It was found that neurofibrillar differentiation in the human spinal cord begins before the end of the fifth week. Primary motor, primary sensory and secondary neurons are present, but functional reflex connections have not been made. All the elements needed for a functional spinal reflex system are laid down by the end of the sixth week. However, muscular development and morphologic connections between neurol structures are still incomplete. Tracts descending from the reticular formation forecast the foundation of an integrative mechanism. In the seventh week peripheral motor and sensory endings of a primitive type are forming, and the first collaterals of the dorsals (sensory) funiculus are making their way into the region from which spring the association neurons. Human embryos of 7 weeks are not quite ready to execute spinal reflex movements. The first spinal reflex arcs are completed during the eighth week.

AUTHORS' ABSTRACT.

THE MORPHOLOGY OF THE HYPOPHYSIS OF AMBLYSTOMA. PAUL GIBBONS ROOFE, J. Morphol. **61**:485 (Dec.) 1937.

The morphologic pattern of the hypophysis and the adjacent hypothalamic regions of young adult salamanders (Amblystoma tigrinum) was studied by means of models reconstructed from blotting paper and microscopic sections. A new term, pars subdistalis, is introduced to designate a discrete portion of the hypophysis which is embedded in the medial and ventral portions of the pars distalis. This portion is constantly present and can be stained differentially by several methods. Its cells are predominantly of one type only, that is, acidophilic, as compared with the surrounding basophilic cells of the pars distalis. Except for size and shape, the other portions of the hypophysis of Amblystoma do not differ from those of other amphibia already described in the literature. The ease with which the hypophysis and the pars subdistalis can be exposed offers possibilities for physiologic investigation.

WYMAN, Boston.

THE NON-CENTRIFUGAL DEGENERATION OF SEVERED PERIPHERAL NERVE. O. SUGAR, J. Neurophysiol. **1**:7 (Jan.) 1938.

Sugar points out that there is much disagreement among histologists as to whether degeneration in the peripheral portion of a severed nerve occurs simultaneously along the entire course of the nerve or whether it takes place centrifugally, progressing from the cut end peripherally. Some attempt has been made to answer this problem by means of physiologic experiments. Sugar made observations on the sciatic nerves of frogs. The cut left sciatic nerves of leopard and wood frogs kept at from 18 to 20 C. lose the capacity to transmit impulses to the attached gastrocnemius muscles thirteen or fourteen days after section. This loss, measured by the height of the muscle twitch, occurs simultaneously throughout the length of the peripheral stump. At from 12 to 15 C. the physiologic degeneration is not complete until the seventeenth day after the cut. Action potentials from these nerves decline and disappear simultaneously throughout the length of the nerve as degeneration progresses. Histologic examination of teased out fibers of degenerating nerves with a modified sudan III and hematoxylin stain shows no linearly progressive myelin degeneration. Discrepant observations by others can be accounted for in terms of the use of stimuli which were inadequate in view of the presence of branches and of the irregular distribution of motor fibers in the sciatic nerve of the frog and of failure to eliminate the area of traumatic degeneration at the cut end of the nerve. These results have been confirmed in rats, in which the loss of indirect excitability occurs from fifty to seventy hours after section.

ALPERS, Philadelphia.

STUDIES ON THE EXISTENCE OF A PARAPHYSIS IN MAMMALIAN EMBRYOS. KNUD H. KRABBE, Brain **59**:483, 1936.

An extensive collection of mammalian embryos was examined for the purpose of determining the existence of a rudimentary paraphysis. In the majority of the embryos there was not seen at any stage a formation which might be regarded as a rudimentary paraphysis. This was particularly true with regard to a complete series of Spermophilus and Vespertilio embryos. In many embryos the anterior wall of the dorsal sac, i. e., the recessus anterior, formed a cupular prominence which might be mistaken for a paraphysis. In 3 mammals there were structures which required more detailed study.

In a 14 mm. embryo of Phascolarctus there was observed at the transition between the anterior part of the dorsal sac and the lamina supraneuroporica, corresponding to the site of the paraphysis in reptiles, a tubular formation issuing from the roof of the brain which was directed backward. It is impossible to prove with certainty that this corresponds to the paraphysis in reptiles. In many vertebrate embryos there are evaginations from the roof of the brain; however, when the diencephalon of Phascolarctus is compared with that of reptiles and when one takes into account the position and development of the evagination, a striking resemblance to the paraphysis in reptiles is evident. In 12 and 14 mm. cat embryos, as in several other embryos, both sides of the dorsal sac had evaginations which pointed forward. Between these was a saccular, thin-walled evagination from the roof of the brain which was possibly a rudimentary paraphysis.

In several human embryos of about 20 mm. (75 days) an outwardly directed evagination was visible at the place of transition between the dorsal sac and the supraneuroporic lamina. The form and position of this evagination indicate that it is a rudimentary paraphysis. It is, however, only a transitory structure, but it is striking that at a certain stage of development even man seems to have this phylogenetically old formation, which has probably disappeared in most other mammals.

SALL, Philadelphia.

MOVEMENTS IN MIDFOETAL LIFE IN THE SHEEP EMBRYO. J. BARCROFT and D. H. BARRON, J. Physiol. **91**:329, 1937.

At 40 days of age the normal sheep fetus shows jerky movements; at 50 days, sustained movements, and at later stages, quiescence. During the quiescent stage exposure combined with occlusion of the umbilical cord produces sustained movements, succeeded by jerky movements and then immobility and death. Between the 50 and the 76 day stage the fetal central nervous system was transected without removal from the uterus at levels ranging from the fourth cervical segment to the diencephalon, and the fetus was examined several days later. The spinal fetus shows spontaneous, active, jerky movements below the level of transection. The fetus sectioned through the midbrain differs from the spinal fetus only in that the higher the transection the less jerky are the movements. Transection through the diencephalon induces movements of sustained type. These results are interpreted to indicate that the fundamental movements are jerky and that they are inhibited by influences arising in the region of the red nucleus, from which they can be released by either asphyxia or transection. Respiratory movements develop at about the 40 day stage as a sequel to other movements, but cannot be induced by asphyxia. After 60 days they become difficult to elicit. On transection through the pons or the midbrain, respiratory movements return and become continuous and jerky; if the section is above the midbrain they are continuous and tonic. These results also are interpreted to indicate release from inhibition from upper levels. The possibility of asphyxia acting at times as a stimulus is not ruled out.

MCCOUCH, Philadelphia.

THE SO-CALLED HYPOPHYSIAL-INTERBRAIN SYSTEM. O. GAGEL and W. MAHONEY, Ztschr. f. d. ges. Neurol. u. Psychiat. **156**:594 (Nov.) 1936.

Twenty animals were used in this experiment (monkeys, dogs and cats). Hypophysectomy was performed in some, and in others the pituitary stalk was severed. In most of the animals sufficient time elapsed to allow for retrograde degeneration. No convincing evidence of retrograde degeneration was observed in the nucleus supraopticus, the nucleus paraventricularis or the nucleus tuberomamillaris or in the nuclei of the tuber cinereum, the nucleus reuniens, the nucleus paramedianus or the nucleus of the mamillary body. In a few cases in which degenerative changes were present other reasons for the degeneration were evident. The authors warn against drawing conclusions from the results of hypophysectomies in dogs because of the comparative shortness of the stalk in these animals and the practical impossibility of removing the body of the pituitary or cutting the stalk without injuring the contiguous hypothalamic structures. No atrophy of the posterior lobe of the pituitary gland was seen after cutting the stalk. No changes were noted in the cells of the superior cervical ganglion after extirpation of the hypophysis.

SAVITSKY, New York.

EXPERIMENTAL INVESTIGATION OF THE RED NUCLEUS, MONAKOW'S TRACT, CENTRAL TEGMENTAL TRACT, ETC., IN RABBITS. T. AGAWA and S. MITOMO, Psychiat. et neurol. jap. **41**:87 (Nov.) 1937.

Stab wounds were made in the midbrain or posterior portion of the diencephalon in rabbits, and sections were studied from thirty to fifty-three days after the operation. The following observations were made: The pars magnocellularis of the red nucleus and Monakow's tract have no relation to the act of standing or righting. 2. The nucleus of Darkschewitsch and the nucleus interstitialis are of most significance for this act. Both these nuclei give origin to the central tegmental tract. 3. The posterior longitudinal bundle has a slight connection with the central tegmental tract. 4. The authors believe that the nucleus of Darkschewitsch and the nucleus interstitialis of the rabbit represent the chief portion of the pars parvocellularis of the red nucleus, since recent studies have shown that in man the central tegmental tract connects the pars parvocellularis of the red nucleus and the inferior olive.

ALPERS, Philadelphia.

Physiology and Biochemistry

THE BIOLOGICAL ASSAY OF THE CARBOHYDRATE METABOLISM HORMONE OF THE ANTERIOR PITUITARY. A. J. BERGMAN and C. W. TURNER, J. Biol. Chem. **123**:471, 1938.

Evidence indicates that a "carbohydrate-metabolizing" hormone is present in the anterior lobe of the pituitary. Tests for the presence of this hormone are based on the ability of pituitary extracts to cause rapid elevation of the dextrose level of the blood in well nourished guinea pigs. A unit of hormone is defined as the minimum amount of extract which when injected intraperitoneally into well nourished male guinea pigs weighing from 180 to 220 Gm. will cause after eight hours an average increase of 50 per cent in the level of the blood sugar of 5 or more animals. Extracts of samples of the pituitary gland from sheep and cattle in 60 per cent alcohol at a p_H of from 9 to 10 contained about 250 units per gram of dried extract.

PAGE, Indianapolis.

FORM OF THE CEREBRAL CHANGES IN POTENTIAL. H. ROHRACHER, Arch. f. d. ges. Physiol. **238**:535, 1937.

In order to determine accurately the shape of the Berger alpha waves, Rohracher recorded them at such a speed that each wave had a length of 40 mm. Two hundred and sixteen ordinates of nine successive waves were mathematically analyzed by the method of Fourier. This analysis led to the conclusion that the alpha waves have the form of a sinus curve.

SPIEGEL, Philadelphia.

ALLEGED CHANGE IN CHRONAXIA OF THE FLEXOR MUSCLES OF THE ARM IN VOLUNTARY INNERVATION OF THEIR ANTAGONISTS. H. H. PODESTA, Arch. f. d. ges. Physiol. **238**:629, 1937.

Bourguignon claimed that on voluntary innervation of the extensor muscles of the elbow or of the hand the chronaxia of the respective flexor muscles is doubled, while on flexion the chronaxia of the extensor muscles remains practically unchanged. He expressed the belief that the high tonus of the flexor muscles prevents the action of the extensor muscles, this being considered the mechanism of reciprocal inhibition. In the present investigation, the chronaxia of the biceps and the flexor carpi ulnaris muscle was determined on voluntary static and kinetic innervation of their antagonists. It was found that the chronaxia is independent of the state of innervation of the muscle studied. The peripheral motor neuron does not show changes in excitability on voluntary innervation detectable by the chronaxia method in reciprocal innervation.

SPIEGEL, Philadelphia.

ROLE OF THE CENTRAL NERVOUS SYSTEM AND THE THYROID IN REGULATION OF TEMPERATURE. B. VON ISSEKUTZ JR., Arch. f. d. ges. Physiol. **238**:787, 1937.

Transverse section of the cervical region of the spinal cord in dogs does not abolish the chemical regulation of temperature, but diminishes it only temporarily. The heat production of the animals is not increased if the temperature of the environment is lowered. The loss of heat, which is considerable, owing to loss of the physical regulation of temperature, is not completely compensated, and the temperature of the animal drops. After a few days the temperature regulation of these animals improves. If one removes the thyroid in such animals the chemical regulation of temperature drops parallel with the decrease in the basal metabolism, so that the animals can maintain a normal body temperture only if kept in an incubator or under a warm blanket. Administration of thyroxin may improve the regulation of temperature. Thus, the thyroid plays an important, but not the exclusive, part in the regulation of temperature. It increases the excitability of the metabolic centers, so that they increase the production of heat. The chemical regulation of temperature is completely abolished in dogs only if all pathways which connect the centers for temperature regulation and the periphery are cut. Besides severance of the cervical region of the spinal cord, one must cut both vagus nerves and must remove both inferior cervical and stellate ganglia. After all these pathways are interrupted the animals become poikilothermic and completely lose the ability to regulate temperature.

SPIEGEL, Philadelphia.

COURSE OF EXCITATION IN SENSORY HUMAN NERVES. U. AUSTER, Arch. f. d. ges. Physiol. **239**:97, 1937.

In order to determine the refractory period in human sensory nerves, two electrical stimuli repeated at various intervals were applied to a finger. The object was to determine whether the sensation elicited by the two stimuli could be distinguished from the sensation produced by a single stimulus. It was found that the first stimulus was followed by a phase of lowered excitability (first relative refractory period), which passed after about 0.4 millisecond into absolute unexcitability (absolute refractory period). The first relative refractory period was explained by the lack of homogeneity of the excitable substance. Since various nerve fibers conduct the excitation with different speeds, a second stimulus may be effective until the slowest fiber has become refractory. The absolute refractory period was followed by the second relative refractory period, which ceased after about 3 milliseconds. After this period two stimuli still elicited the sensation of a single stimulus, which was only more intense. This is explained by the assumption that the refractory period of the centers is longer than that of the peripheral nerves. If the time interval between the two stimuli was increased, the two stimuli might elicit a succession of sensations resembling the phasic course of optic sensations, particularly of after-images.

SPIEGEL, Philadelphia.

ANALYSIS OF RETINOMOTOR PHENOMENA. H. WIGGER, Arch. f. d. ges. Physiol. **239**:215, 1937.

Wigger analyzes the role of chemical and neural factors in the mechanism of the motor phenomena shown by the retinal pigment and cones under the influence of darkness and light. On isolated eyes of goldfishes light produces expansion of the pigment and contraction of the cones; darkness causes the opposite effect. The effect of solutions of different hydrogen ion concentrations on isolated eyes supports the view expressed by Studnitz that the retinomotor phenomena are produced by increase in acidity due to decomposition of cone substance and by a shift to the alkaline side in darkness. Nerves influence the retinomotor phenomena; experiments after section of the optic nerve showed that this nerve has a promoting influence on these phenomena in the same as well as in the opposite eye, while the oculomotor and trochlear nerves have an inhibitory influence on the movements of the pigment and cones. A definite influence of the abducens nerve could not be found.

SPIEGEL, Philadelphia.

A WATER-SOLUBLE FORM OF ACETYLCHOLINE IN THE CENTRAL NERVOUS SYSTEM OF THE FROG. O. LOEWI, Arch. f. d. ges. Physiol. **239**:430, 1937.

It is generally assumed that the substances mediating the nerve impulses to the end organ are liberated on stimulation from a bond, thus becoming diffusible and effective. This view is based on the fact that these mediator substances are present but ineffective in the resting state; in this state acetylcholine is also unaffected by esterase. In studying the central nervous system of frogs, the author found a rather constant content of acetylcholine (between 4 and 5 micrograms per gram of central nerve tissue). Only 20 per cent of this amount (the water-soluble portion) could be extracted by Ringer's solution, while 80 per cent was insoluble in water and unaffected by esterase but could be extracted by alcohol and acids. A large part of the alcoholic extract was ether soluble (lipoid soluble). After being liberated from its bond by alcohol or acids, the water-insoluble part of the acetylcholine became water soluble and also destructible by esterase. It may be inferred that the water-insoluble form of acetylcholine is bound not only to lipoids but also to proteins in the central nervous system. The relationship to the lipoids of the central nervous system indicates the functional importance of the water-insoluble form of acetylcholine.

SPIEGEL, Philadelphia.

TEMPERATURE REGULATION AFTER OPERATIVE REMOVAL OF THE "HEAT CENTER." R. THAUER and G. PETERS, Arch. f. d. ges. Physiol. **239**:483, 1937.

Rabbits were kept alive up to six and a half weeks after complete severance of the brain stem between the diencephalon and the mesencephalon (midbrain animals). Immediately after elimination of the hypothalamus lability of temperature, consisting either of hyperthermia or hypothermia, was observed. This initial thermolability disappeared within a few days. From ten to fourteen days after the operation the animals could be kept at room temperature; the lowest temperature that did not produce disturbances of body tmperature was from 14 to 15 C. (57 to 59 F.). The animals were able to keep the body temperature 25 C. (77 F.) above the temperature of the environment. In 2 midbrain animals spontaneous fever was observed; in a third, fever could be produced by intravenous injection of a nonspecific bacterial preparation (pyrifer). Thus, the ability to regulate the body temperature is not lost after elimination of the prosencephalon and diencephalon, including the hypothalamus.

SPIEGEL, Philadelphia.

EXPERIMENTAL INVESTIGATIONS ON PYRAMIDAL LESIONS IN DOGS AND A STUDY OF CENTRAL REGENERATION. OTTO MARBURG, Jahrb. f. Psychiat. u. Neurol. **53**:164, 1936.

Section of the lateral columns in the thoracic and lumbar portions of the spinal cord was performed in 12 dogs, from 6 to 8 weeks old, under aseptic precautions. Unilateral and bilateral lesions were made. The animals were allowed to survive for from three days to two and one-half months. These periods of survival were selected in order to allow some restitution of function.

The results obtained were similar to those observed in man after war injuries. Regenerative manifestations were not observed except in the posterior roots, and here they were incomplete. What is designated as regeneration consisted of insignificant outgrowths of axons in various directions; as a fact, it was not always possible to tell whether the process was one of regeneration or of degenerative or reactive alteration. In view of the inability to demonstrate definite regeneration in older animals, one is compelled to offer another explanation for the restoration of function in the animals subjected to experiment. According to Marburg, the restoration of function may be assumed to be due to the fact that the pyramidal and pallidal fibers, which terminate to a great extent at a higher level, make connections with intermediate cells which convey the impulses farther down. Although Ziehen expressed the belief that the commissural cells play such a role, Marburg is not prepared to accept this view entirely. Marburg's investigations disclosed that section of the posterolateral columns in the dorsal and lumbar regions is not followed by paresis of the hindlegs, provided the section is limited to the white substance. Paresis of these limbs occurs, however, when the lesion includes the zona intermedia and the central canal. Bilateral section which includes the entire area caudad from the zona intermedia is also followed by paresis. Evidences of regeneration to which restitution of function could be attributed were not observed in animals at this age.

KESCHNER, New York.

INJURIES PRODUCED BY NICOTINE IN THE CENTRAL NERVOUS SYSTEM OF ANIMALS. A. STIEF and S. HUSZÁK, Monatschr. f. Psychiat. u. Neurol. **95**:36 (Feb.) 1937.

Anatomic studies of the central nervous system were made by Stief and Huszák on 5 dogs poisoned by the subcutaneous administration of nicotine. In 1 animal acute poisoning was produced by injection of 1 Gm. of the drug. Clonic and tonic convulsions occurred in two minutes, and the dog died one minute later, with signs of respiratory paralysis. Except for macroscopically visible pallor of the brain, no changes could be demonstrated in the nervous system. Subacute poisoning was produced in another dog by the administration of 10 mg. of nicotine. Death occurred in six hours, after prolonged salivation, vomiting and weakness. Macroscopically the central nervous system showed hyperemia. One animal was given 10 mg. of nicotine daily for approximately three months and was then killed by injecting a large dose of the drug. Gross examination disclosed hyperemia of the central nervous system, a cystic area of softening in the region of the right frontal lobe and basal ganglia, with several smaller foci of softening nearby, and a small necrotic focus in the left caudate nucleus. An animal which was given from 2.5 to 5 mg. of nicotine daily died in twenty-seven days. Grossly, the brain was hyperemic, and there were several small hemorrhages in the white matter. Another animal received amounts of the drug varying from 2.5 to 5 mg. daily for one month and was then killed by exsanguination. No macroscopic changes were observed in the central nervous system of this animal.

In all the animals in which subacute or chronic poisoning was produced microscopic examination of the brain revealed perivascular rarefaction of the nerve cells, outspoken fibrosis and dilatation of the small blood vessels, foci of softening and occasional hemorrhages. The nerve cells of the dentate nucleus exhibited severe changes, chiefly of an ischemic type, but diffuse damage to the cortical

neurons was not noted. The nuclei of the hypothalamus and medulla were well preserved. Noteworthy alterations did not occur in the spinal cord or cervical sympathetic ganglia.

From these observations, Stief and Huszák conclude that nicotine does not have any direct, histologically demonstrable effect on the nerve cells. The pathologic changes are expressions of organic and functional disturbances of the circulatory apparatus. The observations failed to provide morphologic confirmation of Langley's theory that nicotine has a paralyzing effect on the sympathetic ganglia.

ROTHSCHILD, Foxborough, Mass.

Neuropathology

AN ADULT FORM OF FAMILIAL AMAUROTIC IDIOCY WITH CEREBELLAR AND EXTRAPYRAMIDAL SIGNS AND WITHOUT AMAUROSIS. LUDO VAN BOGAERT and PIERRE BORREMANS, Rev. neurol. **67**:618, 1937.

Van Bogaert and Borremans report a case of a disease, beginning at the age of 15 and consisting clinically of severe dementia with attacks of agitation, hyperkinesia of extrapyramidal type, involuntary, stereotyped and apparently purposive movements of the arms and cerebellar disturbances. The man lived to the age of 62. Necropsy showed characteristic ballooning and storage of lipoids in the brain, particularly in the cells of the deep cortical layers and in the corpus hypothalamicum of Luys. Cortical layers IV and VI were diffusely rarefied. The storage of lipoids is believed to differ from that occurring in presenility and in generalized lipoidoses. The patient's genealogic record revealed familial occurrence of this disease.

LIBER, New York.

BULBAR ENCEPHALITIS COMPLICATING DIPHTHERIA. P. SCHRANK, Deutsche Ztschr. f. Nervenh. **144**:281, 1937.

A patient aged 32 had had fever, vomiting and headache for four days. Gait was stumbling; there was nystagmus, but no other definite neurologic signs. A day later he began to regurgitate liquids through the nose and saw double. He died seven days after the onset. A culture from the nose was reported to be strongly positive for diphtheria bacilli. On examination nothing remarkable was seen in the brain except multiple purulent hemorrhagic spots in the floor of the fourth ventricle. These tiny abscesses were made up of leukocytes and lymphocytes, clustered about veins. The brain was fixed in formaldehyde, and thus the possibility of recognition by culture was removed; special stains, however, showed bacteria with characteristic polar bodies. No bacteria could be seen in the cranial nerves. Only 1 similar case has been reported (Sterling).

PUTNAM, Boston.

ACUTE ASCENDING POLYRADICULONEURITIS. A. JUBA, Deutsche Ztschr. f. Nervenh. **144**:290, 1937.

Juba reports the case of a man aged 31 who had severe rhinitis for two weeks. He then experienced paresthesias, beginning in the feet and gradually ascending to the face in the course of two days. He was unsteady and weak. Examination showed absence of deep reflexes and hypesthesia. The weakness increased. There was paralysis of the bladder. He died of pneumonia about eight days after the onset of symptoms. In the peripheral nerves, including the vagus, degeneration of myelin and phagocytosis of fat were already in progress. The process was even more active in the nerve roots. All preparations showed perivascular infiltration with lymphocytes, phagocytes and a few polymorphonuclear cells. The central nervous system showed no abnormalities. According to Juba, the mild infiltrations exceeded the limits of symptomatic inflammation. He compares them with the lesions in the cases reported by Pette and Környey, which were assumed to be

due to a filtrable virus traveling up the nerve sheaths. The author adopts the same hypothesis in his case and explains the more purely degenerative phenomena in chronic cases as due to healing after "autosterilization."

PUTNAM, Boston.

Diseases of the Brain

EPILEPSY: A PAROXYSMAL CEREBRAL DYSRHYTHMIA. F. A. GIBBS, E. L. GIBBS and W. G. LENNOX, Brain **60**:377, 1937.

Knowledge obtained from the use of the electroencephalograph in cases of epilepsy has given a clearer understanding of the pathophysiologic process underlying this condition. It is now known that epilepsy is due to the development of abnormal rhythms in the cerebral cortex; it is a "paroxysmal cerebral dysrhythmia." This discovery places the study and understanding of epilepsy on a different and deeper level and requires reorientation of thinking. In the past few years, by means of the electroencephalograph, the authors made records of about 400 epileptic patients. Seven new facts were obtained as a result of this and previous studies, which the authors now record: 1. Seizures involving the cortex are accompanied by distinct and characteristic fluctuations in the action potentials of the brain. However, several patients who had seizures while under observation showed no abnormality of rhythm during the seizure. The authors believe that in these instances the disordered rhythm involved a portion of the brain other than that for which potentials were being recorded. While it is possible to record the activity of six cortical areas simultaneously, all parts of the cortex are not accessible from the surface of the head, and, more important, disturbances confined to subcortical areas are not recorded. The few seizures which were not accompanied by abnormal cortical rhythms were bizarre in pattern, falling in the group of "epileptic variants." If a patient has a tonic-clonic convulsion during which he shows no abnormalities of cortical activity, he may be either hysterical or malingering, for the disturbance in grand mal involves the entire cortex and is therefore readily detected with electrodes on any part of the head. The absence of electrical abnormalities does not permit a differential diagnosis of hysteria and certain bizarre forms of epilepsy. The presence of abnormalities in the electroencephalogram may, however, demonstrate that in certain cases unexplained muscular jerkings, temper tantrums or moments of abstraction are really minute petit mal or psychomotor seizures. 2. The rhythm which obtains during seizures is distinctive for the three main types: Grand mal attacks have a fast rhythm; psychomotor attacks, a slow rhythm, and petit mal episodes, an alternating fast and slow rhythm. The exact pattern of the seizure tends to be characteristic for each patient. 3. Antecedent to these gross abnormalities of rhythm is the lack in epileptic patients of competent control of cerebral rhythms. Conditions such as excitement, closing the eyes or sleep, which modify the rate of the normal cortical rhythm, place a strain on the rate-regulating mechanisms of epileptic persons which they are frequently unable to meet. The authors believe this accounts for the tendency for seizures to occur on waking or on falling asleep. Seizures which follow emotional upsets, which cause moderate changes in rhythm even in normal persons, are often called "psychogenic." In general, electroencephalograms made from time to time for epileptic persons show more variations than repeated electroencephalograms for normal persons. 4. Some patients have subclinical seizures, which are typical short disturbances of rhythm not attended by subjective or objective evidence of a seizure. Subclinical petit mal attacks are more frequent than grand mal. They are seen usually in the records of patients with a history of very frequent petit mal attacks. However, recorded petit mal lasting for five, ten or fifteen seconds, may occur without clinical manifestations and may be present in patients without a history of petit mal. 5. There is evidence that grand mal may be predicted many hours in advance. 6. In some patients abnormal activity begins in one area of the cortex and spreads to involve

other areas. In a number of instances the abnormal waves of subclinical seizures were entirely confined to a specific area. One such patient was greatly improved after bilateral amputation of the frontal lobes. 7. Electroencephalography has been found useful in determining the value of various methods of therapy without the necessity of waiting for clinical seizures. Because anticonvulsant drugs slow cortical rhythms, they are more effective in grand mal than in other types of seizures. The inhalation of carbon dioxide and the administration of dextrose are effective temporarily in abolishing certain abnormal rhythms. In some patients attention prevents the development of abnormal rhythms.

SALL, Philadelphia.

CORTICAL MONOPLEGIA FOLLOWING HEAD INJURY. P. FELDMANN, Harefuah **12**:302 (May) 1937.

Feldmann reports the case of a man aged 27 who was hit by an iron rod and was unconscious for two or three hours. Immediately after, he was found to have weakness of the left lower limb of the upper motor neuron type and paresis of the right lower part of the face. The muscles of the left shoulder were involved. The more distal muscles of the left upper limb were spared. Association of monoplegia cruralis and involvement of the shoulder muscles corroborates the experimental work of Sherrington and others, who stated that the centers in the motor cortex for the lower limb and the shoulder group lie close to each other and that those for the thumb and fingers lie more inferiorly.

SAVITSKY, New York.

SYNDROME ASSOCIATED WITH "FRONTAL AKINESIA." R. ALMQUIST, Acta psychiat. et neurol. **12**:515, 1937.

Almquist describes the psychiatric and neurologic disturbances observed in a series of 6 cases of a lesion presumably of the frontal lobe. The symptoms and evolution of the condition in all cases were alike. The patients were admitted repeatedly to a psychiatric hospital because of acute episodic relapses of mental and physical symptoms, followed by remissions. In none of the cases could exploration at operation be made, for during acute exacerbations the condition was inoperable and during remissions permission for operation was refused. In all cases the author excluded tumor of the brain and epidemic encephalitis and admitted the probability of a chronic inflammatory process of meningeal origin, due either to severe injury to the head, recorded in 3 of the cases, or to frontal sinusitis, in 2 other cases. The neurologic picture in all cases resembled the frontal syndrome of Gerstmann. The neurologic symptoms consisted of unsteady, tottering gait, arrhythmia of movements of locomotion, retropulsion, opisthotonic crises with a "spontaneous" Babinski sign, forced deviation of the head to one side, imitative synkinetic movements and disturbances in spontaneous orientation of gaze toward the object of fixation. The psychiatric disturbances consisted of a pronounced lack of spontaneous motor impulse ("frontal akinesia") with loss of initiative and passive immobility, without paralysis or contracture, apparent anosognosia, auditory and visual hallucinations and changes in the emotional affective disposition. During relapses the patients were impulsive and irritable, and at other times, quiet and abnormally passive. Almquist assumes a frontal localization of the lesion in all cases.

YAKOVLEV, Waltham, Mass.

Peripheral and Cranial Nerves

THE CLINICAL SIGNIFICANCE OF LUMBAR RADICULITIS AND OF NEURITIS OF THE FEMORAL NERVE. JOHN B. DOYLE, J. Nerv. & Ment. Dis. **87**:283 (March) 1938.

Isolated lesions of the femoral nerve are rare. Doyle reports 5 cases of neuritis of the femoral nerve or its lumbar roots. In the first case there were paroxysms

of pain, weakness and atrophy of the left iliopsoas and quadriceps muscles, anesthesia over the anterior aspect of the left thigh and medial portion of the leg and loss of the left patellar reflex, due to a large fibromyxosarcoma involving the femoral nerve before the departure of fibers to the iliac muscle. In the second case a fibrosarcoma in Scarpa's triangle on the left gave a similar syndrome except that the iliac muscle was not weakened, owing to the escape of fibers to the muscle. In the third case vasospastic phenomena in the feet, with gangrene of a toe, led to bilateral sympathetic ganglionectomy. A week later both femoral nerves were affected, with pain, weakness of the iliopsoas and quadriceps femoris muscles bilaterally, loss of both knee jerks and diminution of sensation over the front of the thighs and the medial aspect of the legs. Trauma was considered the cause, aided perhaps by vascular spasm. In the fourth case right femoral neuritis resulted from diabetes mellitus, with weakness of the iliopsoas and quadriceps femoris muscle groups, sensory impairment over the front of the thigh and loss of the right patellar and both achilles reflexes. In the last case lumbar radiculitis was diagnosed because of pains and paresthesias in the right sacral area, the lateral aspect of the thigh and the medial portion of the right knee, with diminution of the right patellar and achilles reflexes. Doyle concludes that if disease of the vertebral column, spinal cord and cauda equina, as well as toxic or metabolic disorders, can be excluded, tumors in the proximal course of the nerves must be considered. If such signs are unilateral and progressive, surgical exploration is justified.

MACKAY, Chicago.

REVIEW OF A GROUP OF CASES OF EPIDEMIC POLYRADICULONEURITIS. L. VAN BOGAERT, F. PHILIPS, J. M. A. RADERMECKER and T. VERSCHRAEGEN, J. belge de neurol. et de psychiat. **38**:151 (March) 1938.

The authors discuss the type of polyradiculoneuritis which is accompanied by albuminocytologic dissociation in the spinal fluid. This syndrome, which was first described by Guillain and Barré in 1916, may occur in epidemic form in both adults and children. The authors believe that the condition should be considered a specific disease entity, of infectious origin, although repeated attempts to isolate a causative organism have been futile. In the majority of cases the outcome is favorable, without sequelae. The few autopsies that have been performed have definitely established that the condition is a disease entity, not related to acute poliomyelitis, epidemic encephalitis or the acute demyelinating myelitides. In spite of the failure to isolate an organism, the authors believe that the disease is caused by a specific virus. The condition must be differentiated from the forms of interstitial neuritis associated with poliomyelitis, herpes zoster and encephalitis and also from the acute toxic and acute febrile neuritides and Landry's paralysis. The authors think that the term "polyradiculoneuritis with albuminocytologic dissociation followed by recovery" best denotes the characteristics of the malady. They do not favor the term neuronitis, since this should be applied to conditions showing inflammatory reactions in the arachnoid. The term neuritis is also not applicable, since this implies a disturbance limited to the peripheral nerves.

DE JONG, Ann Arbor, Mich.

FACIAL SPASM OF DENTAL AND SINUS ORIGIN. BERCHER and GUILLERMIN, Rev. d'oto-neuro-opht. **16**:183 (March) 1938.

Bercher and Guillermin discuss the pathogenesis of facial spasm on the basis of the observation of 2 cases of intractable type. Both patients recovered after the foci of irritation in the teeth and sinuses were removed. The irritation arose in the sympathetic nerve branches accompanying the alveolar or pulpal arteries, setting off a reflex which reached the trunk or branches of the homolateral facial nerve. In cases of facial spasm, it is important to remove any source of chronic irritation about the face capable of setting up motor disturbances through a chronic pathologic reflex.

DENNIS, San Diego, Calif.

CHANGES IN THE SPINAL CORD IN POLYNEURITIS. FERDINANDO ACCORNERO. Deutsche Ztschr. f. Nervenh. **143**:137, 1937.

Accornero reports the pathologic observations in 4 cases of polyneuritis. The first case was that of a woman aged 52 with ascending polyneuritis involving the cranial nerves. The duration of the disease from the onset of the first symptom was about six months. Histologic studies showed inflammatory polyneuritis, with degeneration of the myelin and axis-cylinders and proliferation of the connective tissue. In the spinal cord there were degenerative changes in the anterior roots and alterations in the ganglion cells, especially in the anterior horns. Similar changes were seen in some of the cells of the posterior horns. There was no inflammatory reaction in the meninges or in the substance of the spinal cord. There were no changes in the posterior roots or tracts of the cord. Similar pathologic changes were observed in the remaining 3 cases. Accornero concludes that the majority of the changes in the spinal cord associated with polyneuritis are secondary to disease of the peripheral nerves and to degeneration of the roots. Primary changes also occur, as manifested by alterations in the ganglion cells of the posterior horn.

MERRITT, Boston.

RELATION OF NEURITIS AND CLIMATE. J. SCHORN and G. SCHALTENBRAND, Deutsche Ztschr. f. Nervenh. **146**:129, 1938.

In a survey of the incidence of "neuritis" (unspecified) and neuralgias, it was found that there is always a maximum number of cases in the winter months. Closer analysis, however, showed other maxima during all the seasons. It was found that these occurred with sudden falls of temperature due to the breaking in of masses of polar air. Rises of temperature appeared to have no influence on the incidence of these diseases.

HOEFER, Boston.

Cerebrospinal Fluid

BEHAVIOR OF DEXTROSE AND CHLORIDES IN THE CEREBROSPINAL FLUID IN THE POSTOPERATIVE PERIOD. G. CANGER and G. RADICI, Arch. ital. di chir. **47**:550 (Dec.) 1937.

From their observations on 18 patients, Canger and Radici found that the amount of dextrose and chlorides in the cerebrospinal fluid is increased during the postoperative period. The variations are not related to the type of anesthesia used and do not parallel those in the blood. Dextrose increases more in the cerebrospinal fluid than in the blood. It increases also if glycemia decreases. However, it never reaches pathologic proportions. The ratio of dextrose in the blood and that in the cerebrospinal fluid is diminished. The chlorides in the cerebrospinal fluid increase, whereas those in the blood plasma decrease. The ratio is diminished. The authors point out that the variations are due to dysfunction of the barrier between the blood and the central nervous system which is concerned in the regulation of the passage of plasmatic substances to the fluid. The functions of the barrier are controlled by stimulation of the chemical substances in the blood, which depends on the more or less intense concentration of these substances, especially proteins, in the plasma. The humoral variations induced by any surgical intervention, especially those concerned with the proteins in the blood, are the cause of dysfunction of the barrier between the blood and the central nervous system with consequent changes in the fluid. The authors believe that the modifications of the cerebrospinal fluid during the postoperative period are not related to the nervous disturbances which may appear during that time.

EDITOR'S ABSTRACT.

RELATIONS BETWEEN CONSTITUTION AND PRESSURE OF THE CEREBROSPINAL FLUID AND FUNCTION OF THE CIRCULATORY AND UROPOIETIC ORGANS IN OLD AGE. G. ZANOTTO and G. SCARAMUZZA, Gior. di clin. med. **19**:32 (Jan. 20) 1938.

Zanotto and Scaramuzza made systematic studies on 23 patients, from 68 to 85 years of age, who had arteriosclerosis, arteritis or renal sclerosis. They found that the arterial blood pressure is increased in old age. It is not related to the pressure of the venous blood or that of the cerebrospinal fluid, which are normal and related to each other. The amount of dextrose in the blood and in the cerebrospinal fluid is increased, with a normal ratio. The amount of albumin in the cerebrospinal fluid and the cytologic reactions of the fluid are normal. The average values for chlorides in the cerebrospinal fluid are almost normal. The amounts of urea in the blood and in the cerebrospinal fluid are increased, with a ratio near unity. The elimination of urea through the urine is diminished, and Ambard's formula is increased in the majority of cases. It is independent of arterial pressure and of the ratio of urea in the blood and that in the cerebrospinal fluid. The increased amount of urea in the blood and in the cerebrospinal fluid depends on the diminished elimination of urea through the urine. Alterations in the pressure or the chemical reactions of the cerebrospinal fluid are due to pathologic conditions which involve the brain or to disorders of the cerebral circulation. They were observed in 6 patients in the authors' group who were suffering from cerebral thrombosis, senile dementia or softening of the brain. EDITOR'S ABSTRACT.

Treatment, Neurosurgery

WATER BALANCE IN NEUROSURGICAL PATIENTS. J. C WHITE, W. H. SWEET and E. S. HURWITT, Ann. Surg. **107**:438 (March) 1938.

In addition to blood lost in hemorrhage, which averages from 500 to 1,500 cc., the patient undergoing a prolonged operation for an intracranial tumor may lose up to 1,000 cc. of water from the skin and lungs. White and his co-workers are concerned with what can be done to reduce this and how the disturbed fluid balance can be restored most effectively. The loss of water vaporized from the skin and lungs can be minimized by (1) the substitution for ether of local infiltration anesthesia and (2) avoidance of the use of too warm covering in a hot operating room and in the ward. Replacement of fluid lost during any major craniotomy is best carried out by constant intravenous administration of a 5 per cent infusion of dextrose in physiologic solution of sodium chloride. The injection should be continued in the ward until not more than 2,000 cc. of fluid has run in. In this way, the interstitial fluid reserve, as well as the electrolytic balance, can be maintained at slightly reduced, but safe, levels. After operation, fluid must be replaced much more accurately in the care of neurosurgical than in that of general surgical patients. A slightly deficient state of hydration is safer in patients after operations on the brain, in order to minimize cerebral edema. In the absence of vomiting or diarrhea, a 5 per cent solution of dextrose in distilled water is the solution preferred for prolonged intravenous administration. In addition to the measured output of urine, feces and vomitus, from 1 to 2.5 liters (quarts) of fluid is lost by vaporization from the skin and lungs in the course of each day. If this insensible loss is not taken into consideration, serious dehydration may develop.

EDITOR'S ABSTRACT.

INTRADURAL ABSCESS COMPLICATING ACUTE MASTOIDITIS WITH SUBPERIOSTEAL ABSCESS IN AN INFANT. G. W. OLSON, Arch. Otolaryng. **25**:693 (June) 1937.

Olson reports a case in which there was recovery from an intradural abscess treated with a derivative of sulfanilamide. An infant aged 13 months had bilateral acute suppurative otitis media with mastoiditis and a subperiosteal abscess on the right side. Simple mastoidectomy was done and a fistula observed in the

superior portion of the bony wall of the canal. Free pus was seen between the tegmen antri and the dura. The bone was removed until healthy dura was exposed on all sides. A discolored swelling, one-half the size of a 10 cent piece, was observed on the dura, with a small fistula through which purulent exudate pulsated. Iodoform gauze was placed in the wound, which was irrigated with the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonic acid in doses of 5 cc. every six hours for two days and twice daily for the following three days. A tablet of sulfanilamide was given by mouth twice daily for twelve days. The postoperative course was uneventful. At no time was there any suggestion of meningeal irritation. The child played and ate normally from the day after the operation. The lesion was classified as an intradural abscess because there were no signs of extradural infection.

HUNTER, Philadelphia.

THE PRESSOR EFFECT OF PROLONGED ADMINISTRATION OF GLYCERIN EXTRACT OF ADRENAL CORTEX. R. G. HOSKINS and J. H. FIERMAN, Endocrinology **21**:119 (Jan.) 1937.

Hoskins and Fierman attempted to determine whether the glycerin extract of adrenal cortex had any significant therapeutic effect on schizophrenia. Seven schizophrenic patients were given by mouth gradually increasing doses of extract of adrenal cortex three times a day for forty day periods, beginning with a dose of 0.65 Gm. and reaching a terminal dose varying from 1.95 to 3.25 Gm., three times a day. Prolonged pressor reactions were noted. In general, the blood pressure gradually increased throughout the course of the treatment from an average of 108 systolic and 67 diastolic to one of approximately 160 systolic and 1 diastolic, but a leveling off was observed in all cases at a dose of about 2 Gm., three times a day. In 2 instances the test was discontinued because of hypertension (170 mm. of mercury). No significant improvement in the mental symptoms could be detected.

PALMER, Philadelphia.

SURGICAL TREATMENT OF BELL'S PALSY. W. M. MORRIS, Lancet **1**:429 (Feb. 19) 1938.

Morris states that if Bell's palsy does not improve with conservative treatment after six weeks, decompression of the bony canal which encircles the facial nerve should be performed promptly. The earliest stage at which operation was performed in the author's series was at the end of the six weeks, while the latest was in a case of bilateral involvement of eight years' duration. He has treated 12 patients since 1936 with 1 unfavorable result. The procedure is that described by Duel and Ballance, who advised nerve grafts in cases in which the facial nerve had been injured during mastoidectomy. Recovery in such cases may occur even up to two years after operation. Decompression should be done promptly when faradic stimulation gives no response or the reaction of degeneration can be demonstrated. The choice of cases creates a difficult problem. Cases in which Bell's palsy has been shown to be due to herpes zoster involving the geniculate ganglion are excluded. The favorable cases are those in which no cutaneous eruption has been shown, the complement fixation test with zoster antigen has given a negative reaction and improvement has failed to appear in six weeks. Hearing tests should be done to determine whether the nerve to the stapedius muscle is involved.

KRINSKY, Boston.

AUTOHEMOTHERAPY FOR PARALYSIS OF THE OCULAR MUSCLES. R. CAMPOS, Riforma med. **53**:1439 (Oct. 9) 1937.

Campos reports satisfactory results from autohemotherapy in 2 patients with paralysis of the ocular muscles following hemiplegia of nuclear origin. The technic is as follows: Twenty cubic centimeters of blood is taken from a vein of the

patient's arm and immediately injected in the gluteal region, which is then massaged for some time. The injections are given alternately on each side of the gluteal region at intervals of two days up to ten injections. The condition of one patient was slowly, but progressively, aggravated during the first month, before the author resorted to autohemotherapy. In both patients complete regression of the symptoms and reestablishment of function were induced in about one month. The treatment is simple and harmless.

EDITOR'S ABSTRACT.

TREATMENT OF SPASTIC TORTICOLLIS. G. SCHALTENBRAND, Deutsche Ztschr. f. Nervenh. **145**:36, 1938.

Schaltenbrand reports 13 cases of spastic torticollis in adults. In 2 cases the disturbance occurred in a father and a daughter and was classified as the result of a hereditary extrapyramidal disease. In 2 cases, and possibly in a third, the disease was postencephalitic. In 1 case, the torticollis was of one year's duration and occurred in a patient 67 years of age with evidence of cerebral arteriosclerosis. In the 7 other cases no cause for the disease was found. Myographic examination in the majority of the cases showed disturbance in innervation of musculature in the arms and sometimes also in the legs. These disturbances did not disappear after operation. In 4 cases, after the entire musculature of the neck was infiltrated with procaine hydrochloride the spastic attacks ceased for at least twenty-four hours. In 4 cases injections of a 0.5 per cent solution of procaine hydrochloride were given for several weeks. In 1 case sixty injections of procaine and alcohol were given during nineteen treatments in four months. In all 4 cases the patients were practically cured and were able to return to their professions. Because of its lack of danger, the author suggests that this treatment be employed before a more radical operation is undertaken. He points out that in cases of progressive encephalitis of hereditary origin the disease does not respond to this kind of treatment, but requires operation.

ADLER, Boston.

TREATMENT OF SCHIZOPHRENIA BY INDUCTION OF CONVULSIONS. R. STÄHLI and O. BRINER, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:649 (Jan.) 1938.

Stähli and Briner report experiences with 120 patients with schizophrenia treated with metrazol. Injections were given three times a week. The initial dose was 5 cc. of a 10 per cent solution. The attack usually came on in from five to twenty minutes. If the seizure appeared at a greater interval the dose was increased. This was important because otherwise incomplete attacks with marked excitement and anxiety resulted. There was no amnesia for the episodes, which made it difficult to obtain the patient's consent to continue the treatment. Dislocation of the jaw was noted a number of times during the convulsions. Dislocation of the shoulder was noted in 1 patient with previous attacks of luxation. Fracture of the scapula was seen during the tonic phase in 2 patients. In a few instances there was transitory arrhythmia, and on 1 occasion persistent auricular fibrillation with mild signs of cardiovascular insufficiency was noted. Rises in blood pressure were recorded a number of times in older patients. An elevation of from 50 to 70 mm. of mercury was not unusual, and 2 patients had a rise of 200 and 170 mm., respectively. This increase in pressure persisted for a few weeks after treatment. Two patients died. In 1, during an attack an embolus broke off from an unrecognized thrombus in the pelvic vein. In another, a hypernephroma and a large struma compressing the trachea were observed.

The results for patients with disease of less than one year's duration were as follows: social recovery, in 17 (50 per cent); improvement, in 3 (9 per cent); improvement, but not sufficient to permit discharge from the hospital, in 8 (24 per cent); and no change in 6. Of patients with disease of from one to five years' duration, 3 (13 per cent) showed social recovery; 16 (65 per cent), improvement in the hospital, and 5 (22 per cent), no improvement. Of patients with chronic disease of over five years' duration, 3 (5 per cent) showed social recovery; 2

(4 per cent), sufficient improvement for discharge; 28 (52 per cent), improvement without discharge, and 21 (39 per cent), no improvement.

Eight of 12 patients suffering from acute or subacute catatonia with excitement and restlessness improved. The patients showing depression and anxiety reacted better than those with irritability. The results for patients suffering from acute catatonia with stupor and negativism were not as good; only 8 of 16 improved. The presence of negativism was a good prognostic sign. Of 14 patients with catatonia for over one year, none made a social recovery; 2 were discharged as improved, and 5 were improved, but not sufficiently to leave the hospital. Of 4 patients with acute hebephrenia, 2 made a social recovery; 1 improved, and 1 did not respond to treatment. One patient with hebephrenia of long standing improved sufficiently to return to work. In 5 of 9 patients with the paranoid form a good remission resulted. One of the 3 patients with dementia simplex was able to return to work; the other 2 improved. Strikingly good results were obtained in all of 8 patients with a late stage of schizophrenia, with onset after the menopause or in the presenile period; every patient returned to work, even those with illnesses of over a year's duration. Of 3 patients with schizophrenia superimposed on mental deficiency 1 showed some improvement; the other 2 were not benefited. Forty-two patients with an advanced stage of over five years' duration were treated, 9 of whom improved; none of these improved sufficiently for discharge. When symptoms recurred, another series of injections resulted in improvement.

SAVITSKY, New York.

LYSATE THERAPY OF MUSCULAR DYSTROPHY. D. M. ZALKAN and R. M. KURZON, Vrach. delo **20**:353, 1937.

Zalkan and Kurzon report the effect of lysate therapy on 14 patients with chronic progressive muscular atrophy. Myomyelohepato-ovarian or testicular (depending on the sex) combinations of lysates were used together with administration of strychnine after the method of Bier and Gehrke. Each patient was given four courses of treatment consisting of twenty injections each. The interval between individual injections was two weeks. Definite subjective and objective improvement was noted in 10 patients. The improvement was noted in the course of the treatment or, more frequently, at the end of or some time after the treatment. There developed a sense of well-being, an increase in energy and working capacity and diminution of fatigue. The gait improved; the patients did not fall as frequently and were able to descend and to climb stairs with greater ease. There were an increase in the muscular power and in the circumference of the extremities. In some of the patients lowering of the threshold of electrical excitability was noted. The improvement lasted from six months to two years. The authors do not claim for histolysates the ability to effect cure in cases of progressive muscular atrophy. However, in view of the utter helplessness of patients with this disease, the improvement they noted is significant. The mode of action of lysate therapy in this disease is not understood.

EDITOR'S ABSTRACT.

INVESTIGATIONS ON THE INTOXICATION THEORY IN DEMENTIA PRAECOX, WITH ESPECIAL REFERENCE TO ATTEMPTS AT TOTAL TRANSFUSION. P. J. REITER, Bibliot. f. læger **129**:287 (Sept.) 1937.

By "total transfusion" Reiter means emptying most of the patient's blood at one session and introducing an equal amount from a number of donors. There are many practical obstacles—the requirement of preferably nine donors of the patient's type for each experiment; a correct diagnosis; an active process, as far as can be established; the patient's physical condition, and consent of the patient's family to the intervention. Attempts at detoxication by "total transfusion" in cases of a grave schizophrenic process have during four years been possible in only 4 instances, 1 of paranoid dementia, 1 of hebephrenia and 2 of catatonia. No

donors were from among the patients' relatives. The results seem to the author to indicate that at least in a considerable number of cases of schizophrenia the intoxication theory is correct; he says that the marked degree of clarification in the second case upholds the theory, which is also supported by the results in the first and third cases. In the fourth case, in which the psychosis was resistant to the "total transfusion," there was marked reaction of the white blood corpuscles in the direction of proliferation of immature cell forms. When careful preparations are made and the operation is performed with the necessary technical skill, "total transfusion" in itself is regarded as relatively safe.

EDITOR'S ABSTRACT.

Special Senses

AURAL VERTIGO. A. J. WRIGHT, J. Laryng. & Otol. **53**:97 (Feb.) 1938.

Wright discusses 73 cases of vertigo resulting from suppuration of the middle ear. The disease results primarily from a lesion not in the middle ear, but in the labyrinth. It is marked by increased irritability of the labyrinth, as shown in the cochlea by hyperacusis and in the vestibule by an abnormal reaction to normal stimuli, such as movements of the head, or to minimal abnormal stimuli, such as some alteration of tension in the middle ear. Focal infection is invariably present, and frequently other lesions, especially chronic iritis, exist. In all cases of aural vertigo treatment by eradication of a septic focus or foci has resulted in complete freedom from vertigo. The author believes that cases of labyrinthine vertigo, which have been regarded as of unknown or doubtful origin, can be grouped together as those of a single disease which he calls "focal labyrinthitis." This disease is an inflammation of the labyrinth. He bases this view on the occurrence of nerve irritation, both auditory and vestibular, signs of tension and progressive loss of function and on the analogy with a known inflammatory lesion, chronic iritis. It is not, in his opinion, the result of disease in the middle ear. That it is secondary to a focus of infection is shown by the invariable presence of such a focus and, to a greater degree, by the arrest, or even cure, of the disease when such a focus is eradicated. This, he believes, is the only hypothesis that explains the many isolated observations in the literature which do not fit into the present somewhat indefinite ideas of its pathologic changes. EDITOR'S ABSTRACT.

LOSS OF VISION IN CASES OF GLIOMA ASSOCIATED WITH SEVERE HYDROCEPHALUS AND SUBARACHNOID METASTASES. T. WERNER, Deutsche Ztschr. f. Nervenh. **145**:266, 1938.

In the first case an ependymoma of the fourth ventricle had caused extreme hydrocephalus. Histologic evidence of injury to the posterior aspect of the chiasm by dilatation of the third ventricle was demonstrated. In the 3 other cases (2 of medulloblastoma and 1 of glioblastoma) the tumor had metastasized into the optic recess, involving the chiasm. Such findings may explain the loss of vision and the primary atrophy of the optic nerve seen in association with such lesions in spite of absence of increased intracranial pressure. PUTNAM, Boston.

ADIE'S SYNDROME. M. DRESSLER and H. WAGNER, Schweiz. Arch. f. Neurol. u. Psychiat. **39**:246, 1937; **40**:50, 1937.

The condition variously known as pupillotonia, myotonia of the pupil or pseudo-Argyll Robertson pupil was described as early as 1902, but it remained for Adie, in 1931 and 1932, to elaborate the syndrome and to demonstrate its frequent association with absence of the tendon reflexes. Dressler and Wagner report observations in 9 cases in which the condition was discovered through reinvestigation of a series of cases previously classified as questionable instances of tabes dorsalis or tabes dorsalis associated with negative serologic findings. The pupillary

disturbance was unilateral in 8 of these cases, as it had been in about 85 per cent of the cases reported by others. The pupil involved in the cases of unilateral involvement was usually the wider. When the reaction to light was tested in the usual manner, the tonic pupil as a rule either failed to react or reacted slightly. In one of the authors' cases there was a slight consensual reaction, and in another the pathologic pupil reacted both consensually and directly to light. In 4 of the 7 cases in which no reaction was shown accurate measurement disclosed dilatation after the patient had been in a dark room for some time; the pupil contracted slowly on being exposed to daylight again. Observations with a slit lamp revealed a slight reaction to light in 6 of the 7 cases. The most characteristic feature in cases of this syndrome is the reaction on convergence. When the patient fixes his gaze on a near object the affected pupil, after a latent interval of variable length, begins to contract. Although contraction is slow, it continues until the previously dilated pupil becomes miotic, and even smaller than the other pupil. When convergence is relaxed the tonic pupil does one of three things: it may continue to contract for a brief period; it may remain miotic for a time, or, as in all the cases reported here, it may begin at once to dilate slowly.

The outline of the pupils was regular in only 2 of the authors' cases. Relaxation after accommodation was slow in 4 cases and was weakened in 2 others. The orbicularis phenomenon, or slow dilatation of the pupil induced by closure of the lids against resistance, was definite in 1 case and questionable in another. Characteristic of a tonic pupil and contrary to the behavior of an Argyll Robertson pupil was the prompt and complete dilatation following instillation of homatropine in all 9 cases; in 1 instance the response of the involved pupil was better than that of the other. Hippus was noted in the tonic pupil in 1 case and in both pupils in another. Changes in the pupillary border were looked for and found in 3 cases, the changes being limited to the affected eye in 4 of these cases and present in both eyes in the others. Slight concentric contraction of the visual field on the involved side was recorded in 1 case.

The achilles reflex could not be obtained even with a reenforcement in 7 of the 9 cases reported; in 1 of the remaining cases the reflex was sluggish on one side. Normal patellar reflexes were elicited bilaterally in only 2 cases, although in the others a slight response could be demonstrated on at least one side with reenforcement or summation. Vegetative disturbances were noted in 7 cases. Subjective visual disturbances, including asthenopia, were complained of in a few of the cases. Several authors have commented on the association of pupillotonia and migraine.

The majority of the patients whose cases have been reported were young women. The ages of the authors' patients ranged from 24 to 64, the majority being of middle age; 7 were women. Although Wassermann tests of the blood yielded negative results in every instance, questionably positive reactions of the spinal fluid were reported in 3 cases, including 1 in which there was a definite history of syphilis. The colloidal gold test showed a slight reaction, of the "parenchymatous type," in another case. Traces of globulin were found in the spinal fluid with either the Pandy or the Nonne test in 4 cases, including 1 in which there was a questionably positive Wassermann reaction. Largely because of the not infrequent confusion with the Argyll Robertson pupil, pupillotonia has not infrequently been attributed to syphilis. It is now generally agreed, however, that syphilis plays no, or at the most a very subordinate, part as the cause of this condition, which is to be regarded not as a disease *sui generis* but as a syndrome owing its origin to various toxic and infectious agents, perhaps also to central or peripheral trauma. It is also generally agreed that the vegetative nervous system is involved in the pathologic process. Although the disorder is essentially benign, it persists, with variations in intensity, for many years, uninfluenced by any known treatment. The authors express the view that the sydrome of Adie is not an uncommon disorder and that because of its frequent confusion with tabes dorsalis statistics on the latter condition should be revised.

DANIELS, Denver.

Diagnostic Methods

THE BLOOD PRESSURE AND PULSE RATE AS AN INDEX OF EMOTIONAL STABILITY. HARRY G. ARMSTRONG, Am. J. M. Sc. **195**:211 (Feb.) 1938.

Armstrong states that the literature contains no study of the relation of the reactions of the cardiovascular system as a whole to the relative stability of the individual person. The data were derived from original examination forms of 700 applicants for flying training in the United States Army Air Corps. The candidates were all men between the ages of 18 and 28. The relative emotional stability of each subject was determined by a study of the personality, by which he was classified as "stable" or "unstable"; 301 (43 per cent) were considered stable, and 399 (57 per cent), unstable. There were a correlation of 0.98 for the stable group and of 0.88 for the unstable group and a general correlation of 0.92 between the relative emotional stability of the subjects and the cardiovascular findings. The majority of the cardiovascular reactions related to those of the blood pressure and not of the heart.

MICHAELS, Boston.

THE KNEE PHENOMENON IN CASES OF INTERMITTENT CLAUDICATION. D. PANTCHENKO, Rev. neurol. **68**:436, 1937.

The knee phenomenon associated with intermittent claudication is tested with the patient in two positions, seated and lying down. In both, the patient crosses the legs, with the diseased leg over the well leg, or, if both legs are involved, with the two legs alternately crossed one over the other. After a few minutes there are pain in the calf of the leg and numbness in the sole of the foot, and sometimes tingling in the toes. Usually there is marked local pallor, and sometimes a change in the local temperature, as perceived by palpation. Of 21 cases of intermittent claudication, this sign was present in 19. In the 2 remaining cases the diagnoses were Raynaud's disease and Buerger's thrombo-angiitis. The sign was not present in 250 patients with disease of the peripheral and central nervous systems. Direct pressure on the popliteal region and compression with a pneumatic cuff did not provoke the knee phenomenon, which suggests that the sign is not a purely mechanical effect but that the neuromuscular apparatus of the involved leg plays a part. Intermittent claudication may be due to vasoconstrictor reflexes originating from painful stimuli in the leg. Thus, after trauma to the leg the pulses in the tibial and plantar arteries of the affected side were absent. The pulses later reappeared, but with each dressing of the wound they disappeared while the patient had pains in the leg.

LIBER, New York.

Experimental Pathology

DOES THE VIRUS OF INFLUENZA CAUSE NEUROLOGICAL MANIFESTATIONS? J. B. NEAL and H. L. WILCOX, Science **86**:267 (Sept. 17) 1937.

During the last several months, Neal and Wilcox saw a number of cases in which an acute infection of the respiratory tract diagnosed as grip or influenza was followed within a short time by the development of various neurologic conditions. In 16 such instances the serum was obtained within from one to three or four months after the infection of the upper part of the respiratory tract. In 14 instances no protective antibodies against influenza were demonstrated in the serums tested by the method of Francis and Magill. In 1 instance the mixtures of serum and virus indicated slight, and in 1 instance partial, protection. In no instance was there complete protection. It is reasonable, therefore to assume that the original diagnosis of influenza or grip had been incorrect in at least 15 of the cases. Further indications that the virus of influenza is not an etiologic factor in cases of encephalitis or encephalomyelitis is afforded by two facts: In a personal communication Francis stated that in experimental animals the virus of influenza does not invade the central nervous system, and Snegireff, in a report

from several state institutions in New Jersey in which epidemics of influenza had occurred, stated that there had been no instance in which encephalitis developed during or after the outbreaks of influenza. It is obvious that further work must be done to confirm or refute this opinion. EDITOR'S ABSTRACT.

EXPERIMENTAL STUDIES ON AXONAL DEGENERATION OF THE CELLS OF THE GASSERIAN GANGLION AFTER SECTION OR EXTIRPATION OF THE BRANCHES OF THE TRIGEMINAL NERVE. HAJIME HOTTA, Psychiat. et neurol. jap. **41**:27 (July) 1937.

Hotta studied the effect of section of the three roots of the trigeminal nerve, section or extirpation of the peripheral branches, extraction of teeth, injection of alcohol and unilateral extirpation of the superior cervical ganglion. He observed that axonal degeneration of the nerve cells in the gasserian ganglion appears in from three to five days and is most pronounced in from ten to twenty days. The nerve cells of the ganglion were composed of two main groups: the ophthalmic-maxillary and mandibular groups. Section or extirpation of a peripheral nerve resulted in degeneration of fewer cells than section of the central root. After extirpation of the palatine nerve changes were observed only in the small nerve cells of the ganglion. Extirpation of the auriculotemporal nerve caused degeneration of the cells; this was regarded as the cause of dental otalgia. Extraction of teeth resulted in degeneration of cells in the ganglion. Hotta observed no cells of sympathetic origin in the gasserian ganglion. He concludes that there is a definite relationship between the size of the ganglion cells and their function. Thus, the large nerve cells in the ganglion were found to be concerned with touch, whereas the medium and small cells were concerned with pain.

ALPERS, Philadelphia.

Diseases of Skull and Vertebrae

THE ROLE OF THE HYPOPHYSIS IN CRANIAL OSTEOMYELITIS, PETROSITIS AND SINUS INFECTIONS. G. LEVENE, L. F. JOHNSON, R. M. LOWMAN and E. G. WISSING, Endocrinology **22**:521 (May) 1938.

Levene and his associates believe that the development of cranial osteomyelitis of sinus origin and of petrositis is dependent on the blood supply and the architecture of the skull. Infections within the frontal sinus are provided with adequate avenues of extension along and within the veins draining the middle and inner tables of the skull. The architecture of the skull is discussed under headings relating to the various functional levels of the anterior lobe of the pituitary gland. Type 1 is found in acromegaly. Type 2 is due to an acquired postadolescent deficiency of the anterior lobe, which results in the absence of diploic expansion. This type is frequently associated with obesity. The sinuses and the mastoid cells are poorly pneumatized; the skull is dense and hard; the petrous pyramid is sclerotic, and the tip is nonpneumatized. Type 3 is due to overactivity of the anterior lobe of the pituitary gland, followed by hypofunctional involution. In this type the diploe is expanded, and the paranasal sinuses and mastoid cells are hyperpneumatized. In addition, however, there is secondary sclerosis beginning in the inner table and extending into the diploe. Frequently, there are patchy deposits of calcium on the inner table. The changes are most marked in the frontal bone. These changes, the authors believe, indicate the advent of a variable degree of failure of the anterior lobe. Type 4 is associated with a congenital or preadolescent deficiency of the anterior lobe, which produces the clinical type recognized as the pituitary dwarf. There is absence of diploic expansion, so that the outer and the inner table are in close approximation. As a result, the vault is thin, hard, dense and nonvascular. The paranasal sinuses and mastoid cells are poorly pneumatized, and the petrous pyramids are dense and cancellous. The frontal sinuses are frequently absent, and the cranial sutures remain patent. The face

and jaws are small, and dentition is delayed. From a study of more than 6,000 cases it has been concluded that cranial osteomyelitis of sinus origin and suppuration of the petrous apex occur only in types 1 and 3. These types are associated with hyperactivity of the anterior lobe of the pituitary gland. The incidence of sinus infection is greater in types 1 and 3. The authors call attention to the necessity of considering the types and structure of the skull described in the treatment of infections of the paranasal sinuses and the mastoid, and they believe that endocrine factors play an important role in the development and progress of these conditions.

PALMER, Philadelphia.

PAIN LOW IN BACK AND "SCIATICA" DUE TO LESIONS OF INTERVERTEBRAL DISKS. J. S. BARR, A. O. HAMPTON and W. J. MIXTER, J. A. M. A. **109**:1265 (Oct. 16) 1937.

Barr, Hampton and Mixter believe that with the present state of knowledge an accurate clinical diagnosis of ruptured intervertebral disk in cases of pain low in the back cannot be made and that one must rely on roentgen studies after the subarachnoid injection of a contrast medium to verify clinical suspicions. Iodized oil should not be injected into the spinal canal of every patient suffering from "sciatica." Prolonged, adequate, conservative orthopedic care should be insisted on in every case of suspected rupture of an intervertebral disk before iodized poppyseed oil is used. Injection of saline solution or procaine hydrochloride, manipulation and fasciotomy may be included as "conservative" measures. If these fail to relieve the sciatica, the diagnostic use of iodized oil is indicated before lumbosacral or sacroiliac fusion is resorted to, particularly if the total protein in the spinal fluid is elevated. The operation (laminectomy and spinal fusion) is formidable and should not be advised except on the clearest indications and after the use of conservative measures have failed to give relief. The technic of examination with iodized oil is exacting, but in competent hands the accuracy of diagnosis is high. Local arachnoiditis with matting of the nerve roots has been observed in association with ruptured disk in at least 3 cases. It is believed that it may have been caused by localized hemorrhage or trauma to the roots and meninges at the time the disk was ruptured. In 2 cases in which ruptured disk was suspected, the condition proved to be arachnoiditis without evidence of ruptured disk. It may be that the same sort of injury may cause either of the lesions or a combination of the two.

EDITOR'S ABSTRACT.

LOW BACK PAIN DUE TO HERNIATION OR RUPTURE OF INTERVERTEBRAL DISK INTO SPINAL CANAL. F. L. SIMONDS, Minnesota Med. **20**:456 (Dec.) 1937.

Simonds believes that pain low in the back due to herniation or rupture of the intervertebral disk into the spinal canal is more common than is generally recognized. In the earlier cases the differential diagnosis lay between tumor and ruptured disk and all studies were made on patients showing marked neurologic signs. As the work advanced, diagnosis was possible in many cases in which pain was practically the only symptom. Chondroma, enchondroma, achondrosis and traumatic rupture of the intervertebral disk undoubtedly represent a similar or identical pathologic process. The age in the cases reported varied from 20 to 64 years, and the incidence in men was about five times that in women. The condition occurred in persons from all walks of life, and a definite history of antecedent trauma was obtained in only 50 per cent of cases. It is reasonable to assume that the cause must be a jackknifing type of injury not sufficiently severe to crush a vertebral body, yet violent enough to injure the disk, with protrusion of a small piece into the spinal canal. Pain was the first symptom in every case. The pain was usually described as an ache in the lower part of the back, usually to one side or the other, becoming paroxysmal on turning, stooping, coughing or sneezing, whereon it radiated outward over the buttock and down the back of the

thigh and at times the back of the leg also. Not infrequently the pain commenced in the midline and radiated down the backs of both thighs, but unilateral distribution was the rule. Numbness and paresthesias frequently alternated with or replaced pain. Tenderness even on gentle percussion over the lower part of the spine, lumbosacral ligaments and sacro-iliac joints was commonly present, and on examination the lumbar muscles were found in protective spasm. The sole abnormality in the reflexes noted in most cases was loss of the achilles jerk on the affected side, or on both sides in cases of bilateral involvement. Studies on the spinal fluid showed an increase in the protein content as the only significant change in many instances, and for the most part this was not excessive. In the majority of cases the condition resembled back strain, lumbosacral or sacroiliac strain or sciatic neuritis. Hypertrophic arthritis was frequently a mistaken diagnosis. Roentgen examination as a routine with the aid of subarachnoid injection of iodized poppyseed oil (5 cc.) is the only method by which definite diagnosis may be made. The characteristic defect is produced by a mass ventral to the dural sac, to one side of the midline, and is usually seen best on the posterior-anterior or the oblique view.

EDITOR'S ABSTRACT.

CHANGES IN THE INTERVERTEBRAL DISCS FOLLOWING LUMBAR PUNCTURE. F. J. MILWARD and J. L. A. GROUT, Lancet **2**:183 (July 25) 1937.

Milward and Grout describe the clinical features and roentgenographic findings in the cases of 5 patients operated on under spinal anesthesia, who complained at varying intervals after operation of pain in the back and occasionally of pain in the lower limbs. The anesthesia used was 1:1,500 procaine hydrochloride, injected through the second, third or fourth interspace with a fine steel needle. All the patients complained of severe pain in the back, which either partially or completely prevented them from walking or sitting. In all the cases the lumbar portion of the spine was held rigid in a flexed position by muscular spasm. There was marked tenderness over one or all of the spinous processes of the second, third and fourth lumbar vertebrae. In 1 case there was no latent period. The latent period in the others varied from three weeks to six months. Roentgen examinations in all the cases showed the following changes: (1) progressive arthritis localized in one intervertebral joint; (2) loss of joint space, and (3) new bone formation joining the articular edges of the bodies of the adjacent vertebrae. When the condition was recognized, the treatment adopted was fixation of the lumbar portion of the spine in extension with a full length ambulatory plaster jacket, as in treatment of compression fractures. The three men returned to work free from pain, but with some limitation of movement.

The authors believe that the most satisfactory theory is the assumption that the condition is due primarily to injury to the intervertebral disk, with secondary changes in the vertebral bodies.

WATTS, Washington, D. C.

OSTEOCLASTIC TUMOR OF THE PETROUS BONE. J. A. RAMADIER and A. TOURNAY, Rev. d'oto-neuro-opht. **15**:29 (Jan.) 1937.

The case reported is interesting because of its rarity and the surgical steps which led to the correct diagnosis and use of roentgenotherapy. Osteoclastic tumor, wrongly classed among the sarcomas, is not truly malignant, since it shows no tendency to recur or to form metastases. No case in which there was localization in the petrous bone has previously been recorded. A woman aged 36, suffered from an illness which began in August 1933 with neuralgic pains in the right hemicranium, radiating to the neck and shoulder. Vertigo, tinnitus and deafness in the right ear next appeared, followed by peripheral paralysis of the facial nerve on the right side and, later, vomiting. The pains were characterized by amelioration in the morning and increasing severity later in the day, the severity lessening during the night. Lumbar puncture caused almost complete disappearance of the neuralgia. Examination revealed complete cochleovestibular paralysis of

the right ear and a tympanic membrane of normal appearance. The results of a neurologic examination were normal, except for the seventh and eighth nerves. There were no signs of cerebellar disturbance. The Wassermann reactions of the blood and spinal fluid were negative. A diagnosis of tumor of the cerebellopontile angle was made, and the region was exposed. No tumor or evidence of arachnoiditis was discovered, but an area of softening of the posterior wall of the petrous pyramid, near the internal auditory meatus, was observed. A mastoidectomy, performed two months later, disclosed a spot of softening in the anterior part of the attic, which was curetted, and a mass containing the superior semicircular canal was removed. Exploration of the anterior face of the petrous bone revealed normal dura and osseous cortex. A course of roentgenotherapy resulted in apparent cure of the disease.

Two series of roentgenograms were made. The first, made before operation, showed destruction of the inner half or two thirds of the petrous bone; the second, made after the operations, revealed repair by excessive recalcification.

DENNIS, San Diego, Calif.

HYPEROSTOSIS OF INTERNAL ASPECT OF FRONTAL BONE. M. RASO, Folia med. **23**:903 (Sept. 15) 1937.

Raso performed necropsies in 13 cases of hyperostosis of the internal aspect of the frontal bone (Morgagni syndrome). The condition is more frequent in women than in men. In the present group it was associated with virilism in only 1 case and with obesity in another. None of the patients suffered from hypophysial or endocrine disorders. The microscopic picture varies according to the phase of evolution of the condition in which the patient dies. When the pathologic process is in evolution there is intense development of fibrous connective tissue through the thickness of the frontal bone, which is followed by formation of active osteoblasts. When the process is established evolution stops, and reabsorption of the bone, which is characteristic of old age, takes place. The author reviews the etiopathogenic theories which trace the disease to endocrine disorders, cerebral atrophy, formation of adhesions between the meninges and the bone, disorders of calcium metabolism, pathologic local disorders as shown by Paget and inflammation and disorders of general and local circulation. He believes that local inflammation, secondary to that of the paranasal pneumatic cavities, and local circulatory disturbances are the most plausible etiopathogenic factors.

EDITOR'S ABSTRACT.

NONINFLAMMATORY RHEUMATISM OF THE SPINAL COLUMN (SPONDYLOSIS DEFORMANS). H. HENNES, Med. Welt **11**:1676 (Nov. 27) 1937.

After he has pointed out that rheumatism of the spinal column becomes manifest in several forms which he lists, Hennes gives attention to the degenerative forms, particularly spondylosis deformans, which is the most frequent disorder of the spinal column. As in degenerative articular rheumatism, the functional factor is probably the most important; but other defects, such as faulty nutrition, poor general condition and faulty exertion, may play a part. The decisive factor is that the functional use exceeds the functional capacity. The changes in the vertebral body involve the shape as well as the internal structure. The body shows an increased "waist formation" and is flatter. Proliferations on the edges seek connection with the adjoining vertebrae and may embrace the intervertebral disks. Thus, there develop the roentgenologically visible formations in the shape of points, notches, beaks and clasps. Since wear and use play a part in the development of this form of spondylosis, it is comparatively rare in patients below the age of 40. With increasing age the changes become more frequent. Roentgenograms of the spinal column of persons beyond the age of 60 nearly all reveal such changes. The lumbar region is most frequently involved; then follow the cervical and the thoracic portion. The extent of the roentgenologic changes does

not necessarily correspond to the seriousness of the complaints. There are patients with severe changes who have only slight complaints. The chief symptoms of the disorder are pain and the resulting restriction of movement. All the dependent muscles and nerves are affected. If the cervical portion of the spinal column is involved, there may be pains in the region of the shoulders and neck, which may radiate into the arms and behind the ears. In case of changes in the thoracic region, intercostal neuralgias are often complained of; in case of lumbar changes, pains in the lumbar and sacral regions and in the legs are chiefly mentioned. If the patient rests and refrains from exertion, the pains usually subside. Clinical examination reveals stiffness in gait and posture. The spinous processes are usually sensitive to percussion. The musculature of the back is often painful and rigid. For treatment, Hennes suggests rest and the application of heat, baths and radiation. In order to insure lasting results for these treatments, the underlying irritation must be eliminated. The physician should investigate the patient's occupation and, if necessary, should suggest a change in work. In discussing the differential diagnosis of spondylosis deformans, the author stresses the differentiation of chronic inflammatory rheumatism of the spinal column (spondylarthritis ankylopoietica), with which it is most readily confused. He lists in opposite columns the characteristic symptoms of the two conditions.

EDITOR'S ABSTRACT.

CAVERNOUS HEMANGIOMAS OF THE VERTEBRAL COLUMN WITH SYMPTOMS OF TRANSVERSE MYELITIS. A. S. YUZHELEVSKIY, Vestnik khir. **52**:164, 1937.

According to Yuzhelevskiy, hemangiomas of the bones, including those of the vertebral column, are not rare lesions in postmortem sections. They are, however, seldom recognized clinically. This is even more true of hemangioma of the body of the vertebra causing symptoms of compression of the spinal cord. The literature contains only thirty-four cases of this type, described by thirty-two authors. In only half the cases was the diagnosis made before operation or necropsy. Lack of knowledge of the clinical symptoms and of the roentgenologic appearance is responsible for inability to recognize cases of this lesion. The author reports three instances (the largest number thus far reported by one observer) of identified vertebral hemangioma associated with symptoms of transverse myelitis. In one case the tumor involved the body of the first lumbar vertebra; in the second, that of the fifth thoracic vertebra, and in the third, that of the eleventh thoracic vertebra. In all three cases the clinical syndrome of transverse myelitis was presented. The diagnosis in the first two cases was arrived at during the operation, while in the third it was made before the operation, on the basis of the course of development of the disease and the roentgenologic appearance of the vertebra, which the author considers to be characteristic for this condition. The bony structure of the involved vertebra presents a grossly cellular, spongy appearance, with numerous clear spaces divided by fairly thick trabeculae containing lime. The intervertebral disks are not involved. Roentgenologically, the lesion must be differentiated from giant cell tumor, tuberculosis of the vertebra, osteoporosis, syphilis, myeloma, metastatic carcinoma and hypernephroma, osteoma, Kümmell's disease, osteomalacia and gout. The author considers the roentgenologic appearance of hemangioma sufficiently characteristic to permit of correct diagnosis. His second patient had, in addition to the hemangioma of the body of the vertebra, an extradural hemangioma involving the epidural connective tissue. All three patients made a clinical recovery. When the tumor cannot be radically removed because of its localization in the body of the vertebra, a decompression laminectomy with postoperative roentgen or radium therapy will be of benefit in most cases. The importance of clinical recognition of the lesion depends on the necessity for operative intervention, as well as on offering the surgeon the possibility of instituting prophylactic preoperative measures, particularly with a view to the occurrence of profuse hemorrhage.

EDITOR'S ABSTRACT.

Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

MEYER SOLOMON, M.D., *President, in the Chair*

Regular Meeting, April 21, 1938

SOMNOLENCE PRODUCED BY ELECTRICAL CURRENTS IN THE BRAIN. DR. FRANK HARRISON (by invitation).

A steady direct current, an interrupted direct current, with the rate of rise and fall of intensity too slow for stimulation, and the modified interrupted direct current advocated by Hess were used in a study of the interior of the brain of the waking cat. Nonstimulating currents which produced lesions in the lateral hypothalamic area produced somnolence. Stimulating interrupted direct currents evoked pupillodilatation, respiratory changes and excitement and rage reactions, depending on the position of the electrodes, but never produced somnolence. The regions of the brain studied were the hypothalamus, the thalamus, the junction of the hypothalamus and the thalamus, the anterior commissure and the septum pellucidum. It was concluded that somnolence can be produced by lesions in the lateral hypothalamic area, especially of the posterior part, but not by stimulation of any of the regions studied.

INSULIN SHOCK THERAPY: REPORT OF ONE HUNDRED CASES. DRS. CHARLES F. READ, GERT HEILBRUNN and ERICH LIEBERT, Elgin, Ill.

Of the group of schizophrenic patients at the Elgin State Hospital who had been ill from one to six months, 87 per cent recovered, and 6 per cent improved markedly. Of the second group, patients ill from six to eighteen months, 65 per cent returned home; of the third group, patients ill more than eighteen months, only 10 per cent improved sufficiently to return home; there were no recoveries.

The Sakel technic was modified to some extent. Deep shock in which the reflexes were abolished was not used, and shocks were made as short as possible. In a few cases they were entirely avoided. Experiments on animals have shown that damage to the brain is directly proportional to the amount of insulin given. Antibodies in response to the presence of white matter of the brain can be demonstrated in the blood serum after several weeks of treatment. Sensitization was observed in 70 per cent of patients treated. Often the initial dose could be gradually, or even abruptly, reduced to an end point of 40 per cent of the original shock dose. Vasoconstrictor substances reached their highest point an hour after injection in patients who passed into shock. In the patients who did not have shock these substances continued to rise sharply even after the first hour. Experiments on animals have demonstrated that insulin is not destroyed by the blood serum.

There was a temporary change in the electrocardiogram. Insulin, when covered by dextrose, did not damage the brain (in animals), but produced electrocardiographic changes in human subjects. Hemiplegias and other neuropathologic symptoms were observed after shock, but usually were temporary. One patient showed mild residual signs of a lesion of the upper motor neuron type several weeks after treatment. Epileptiform seizures were observed in 34 of each 100 patients treated. The seizures had no influence on the recovery and were not desired, although they were rarely dangerous. The percentage of convulsions in the groups in which treatment failed was practically the same as that in the groups which recovered. Five of 54 patients who returned home had a relapse. Two of

these, when treated again, recovered promptly. Two have not responded and 1 is in another hospital.

It is believed that the second series of 100 patients to be treated will show about the same immediate results for the respective groups based on the duration of illness. Only time will demonstrate the "long pull" results.

DISCUSSION

DR. CHARLES F. READ: Various staff members have been associated with us in this treatment. Much credit should be given to Dr. Ruth Sternlieb for her assistance. She came here from the Münsingen Clinic, about eight months after Dr. Heilbrunn. Dr. Arthur Weil, while abroad, arranged for them to come to Elgin.

Much has been said at various times as to the size of the personnel needed for a unit in insulin treatment. Exaggerated statements have been made as to the number of physicians and nurses required. We now have a unit of forty beds in four closely adjoining sections, manned by from three to four physicians, two graduate nurses and six attendants. Well selected patient helpers are of great assistance.

My associates and I realize that there are at least three uncertain factors in obtaining the anamneses. First, the heredity is not always accurately stated; perhaps this is not important. Then, one often does not have a good description of the patient's personality before the psychosis began. Sometimes we have determined that the patient made merely a social recovery when the family insisted that he was entirely well. The actual date of onset is too often in doubt. These points all have to do with evaluation of the result of this method of therapy in the individual patient. The diagnosis in this series of 100 cases and the results of treatment have been passed on not only by the physicians in charge of the unit, who may be influenced by their own desires, but by a considerable number of the staff as well. I myself saw practically all the patients and agreed with the consensus of the staff. We have delayed this report until we had a sufficient number of cases on which to base a reasonable conclusion.

DR. ARTHUR WEIL: It is gratifying to know that Dr. Heilbrunn and his associates, in the practical application of insulin treatment, drew conclusions similar to those derived from their experiments on animals. By treating patients individually and trying to obtain maximal benefit with a minimal amount of insulin, it should be possible to secure therapeutic results with total doses of less than 50 units per kilogram of body weight. By such careful medication severe cerebral damage can be avoided.

It was of great interest to hear of the demonstration of lipoid antibodies following insulin treatment. This proves that during treatment organic changes take place in the central nervous system, with liberation of lipoid substances, which act as antigens.

DR. A. A. LOW: At the Psychiatric Institute my associates and I studied recently a series of cases in which we organized the patients under a thorough follow-up system. They meet twice a month, and between the meetings we keep close contact with them. Our results are not as favorable as we originally expected. Some patients had to be readmitted for treatment; others maintained an adjusted life in the community, but had no insight; a third group recovered insight but failed in practical adjustment. When we applied our criteria of (1) insight, (2) abandonment of symptoms and (3) unsupervised activity in the community, we found that about 25 per cent of patients treated with metrazol or insulin showed good recovery. If one included social recoveries, the percentage was raised to about 35. When we examined our patients of former years we found that the recovery rate from 1932 to 1936 was about 15 per cent. The farther the follow-up investigation went back the higher was the rate of recovery. In other words, the condition of patients discharged in a certain year continues to improve, contrary to the common assumption that the rate of recovery drops with each year. Comparison of the rate of posttherapeutic recovery of 25 per cent with the rate of spontaneous recovery of 15 per cent reveals an increase of

10 per cent of undoubted recoveries, which is an advance; I do not think there is occasion to belittle the results. With our system of rotation treatment, which will be reported on shortly, we have found that if we add insulin therapy to treatment with metrazol and narcosis and induction of fever to both, the rate of recovery rises to about 40 per cent; moreover, half the patients consist of persons who had been sick for more than one year.

DR. J. KASANIN: I wish to compliment Dr. Read and his staff on this excellent presentation. I notice that Dr. Heilbrunn avoided any comparison with metrazol, and I should like to ask how the results in this extraordinarily optimistic study compared with those obtained with metrazol.

DR. GERT HEILBRUNN: What Dr. Low has said confirms the results reported by Georgi and Strauss that the use of both insulin and metrazol in some cases increases the percentage of cures.

DISTURBANCES IN CONCEPT FORMATION IN SCHIZOPHRENIA. DR. JACOB KASANIN and DR. EUGENIA HANFMANN.

In certain fields of neurology and psychiatry there is much to be gained from the application of similar methods of investigation. This holds true especially in conditions in which there is gross impairment of the function of speech and language. One finds such impairment, on the one hand, in a group of organic conditions called, somewhat loosely, aphasia and, on the other, in many so-called functional diseases, especially schizophrenia. Hughlings Jackson noted that in aphasia the damage is not so much in dropping out words or in their incorrect usage but in the whole field of language. "To speak is not simply to utter words, it is to propositionise. A proposition is such a relation of words that it makes one new meaning. Single words are meaningless and so is any unrelated succession of words. The unit of speech is a proposition. Loss of speech is therefore the loss of power to propositionise." Jackson postulated that in a breakdown of higher centers, such as is seen in aphasia, propositional speech suffers most severe disturbances, with the retention, however, of lower forms of speech, which he described as automatic or emotional. Speech, then, is not merely a motor phenomenon or a reflex act but a product of the complex mechanism involved in the functions of thought, intellect and symbolic expression. It offers a key to understanding of the intellectual functions and of their impairment.

In schizophrenia there is a varying degree of intellectual involvement, which in some cases may be negligible, while in others it manifests itself as grave dementia. Early descriptions of the disease emphasized involvement of the intellect. One has only to recall the original description of dementia praecox by Morel, in which he reported the case of a boy who was one of the brightest in his class but who as a result of the disease forgot all that he had learned. A kind of inactivity bordering on stupidity replaced the former activity of the child. He described how the boy progressed to unrecoverable dementia; this description gave origin to the term as well as the concept of dementia praecox. More specific reports of intellectual involvement in cases of schizophrenia have stated that one finds in varying degrees incoherence, irrelevance, neologisms, short-circuiting ideas, lack of coordination and correlation and various disturbances of association.

Formal psychologic studies of intellectual involvement associated with schizophrenia have shed little light on the problem, although recent investigations with the Rorschach test have yielded findings with suggestive implications. Tests measuring intelligence were usually applied in studying the intellectual involvement in cases of schizophrenia; although it has been possible to obtain quantitative data, they throw little light on the nature of the problem. If a patient gives an individual or a bizarre response he does not receive credit because of the unorthodox nature of the response. This lowers his score without telling much about the patient himself. In fairness to psychologists, it should be said that the results of intelligence tests and the scores obtained are not held to be representative of the patient's intelligence or the degree of intellectual involvement.

In spite of the great interest in the nature of the dementing process of schizophrenia, no reply could be given to the problem until light was thrown on it from two sources: first, through the advances made in genetic psychology, and, second, through the study of the thought processes of primitive people. Together with many others, Meyer Gross noted that the behavior of schizophrenic patients is much like that of children at play. A child when playing acts much like a schizophrenic person, only he is able to return quickly to the world of reality. Bleuler noted long ago that a schizophrenic persons thinks much like a primitive person, but it remained for von Storch to show in a masterly essay the close identity of schizophrenic thinking with the thinking of primitive people.

With regard to language and thought, von Storch returned to Schelling's idea that the oldest language of the world contained nothing more than sensory images for ideas. He pointed out that all thought was originally in the form of sensations and that the thinking of modern man has gone far from the perceptual foundation in which it originated. Thinking people have the abstract ideas with understanding and reason, in addition to the perceptual basis. For example, when one thinks of the word "mammal" he thinks not only of a particular animal but also of a class of animals which are nurtured on mother's milk. As White pointed out, the thinking of modern man proceeds from feeling, concreteness and perception in the direction of reasoning, differentiation and abstraction. In an essay on schizophrenic thinking, White pointed out that one must assume and take for granted that in schizophrenia one is dealing with a regressive process. Once one accepts that, one can easily see how the thinking of a schizophrenic person closely approximates, on the one hand, the thought processes of a child and, on the other, the prelogical thought of the primitive tribesman.

As a matter of fact, this concept of regression was introduced into the field of psychopathology at a much earlier day by Hughlings Jackson. As mentioned, Jackson observed that in cases of aphasia there is more than mere loss of memory for words. He noted that the whole personality and the behavior of the subject had changed and postulated the breaking down of higher levels. With remarkable insight, he stated that in aphasia there is loss of capacity for what he called propositional speech — that is, speech conveying ideas rather than pure emotions. A further extension of this idea was developed in the writings of Kurt Goldstein. He stated that there are two attitudes on the part of man toward the world in general. In one attitude the individual man thinks concretely and is realistic and literal. Such a person, when he speaks of "table" means not tables in general but the particular table which comes to his mind. He is far from the field of generalizations or abstract ideas. In the other attitude there is the capacity for abstraction, so that thoughts are directed not toward any individual object but toward the general. Such a person either can think concretely or, on the other hand, can form abstract judgments and ideas. This capacity of generalization and classification is what Goldstein called categorical thinking. In concrete thinking language does not play much role. The person with concrete thinking uses words which apply particularly to the individual subject, such as "strawberry red" and "sky blue." In other words, objects are described in a roundabout way. It was Goldstein who noted that in aphasia there is regression toward a more primitive, concrete type of thinking, with loss of the capacity for categorical thought. To differentiate between categorical and concrete thinking is not always easy, as words are used in both types of thinking. That is why Goldstein and his collaborators used a number of ingenious experiments to demonstrate the actual reduction of categorical thinking in patients with cerebral injuries.

The thinking defect of schizophrenic patients already cited was described by von Storch and others on the basis of general clinical observations and impressions. It remained for the Russian investigator Vigotsky to introduce into this field an experimental method which permitted more exact and objective determination of the type of thinking of schizophrenic patients and comparison with the thinking of normal subjects and of other groups of patients.

In devising this method, Vigotsky was led by the idea that in order to discover a slight impairment in categorical or conceptual thinking one should test the process of formation of new concepts rather than the conventional use of previously acquired ones. Since words in the course of their normal development have become vehicles of concepts, patients in continuing to use them still seem to operate with concepts, although actually their conceptual thinking may be impaired. Therefore, to test effectively the level of conceptual thinking, Vigotsky (Hanfmann, E., and Kasanin, J.: A Method for the Study of Concept Formation, *J. Psychol.* **3**:521-540 [Dec.] 1936) introduced a test which requires the subject to form artificial concepts for which language has no adequate designations.

Since our investigations were made with the help of this test, we shall describe it here in some detail. The experimental material consists of twenty-two wooden blocks varying in color, shape, height and size. There are five colors, six shapes, two heights—the tall and the flat blocks—and two sizes of the area at the top—the large and the small blocks. On the under side of each figure, which is not seen by the subject, is written one of the four nonsense words: "lag," "bik," "mur" and "cev." Regardless of the color and shape, "lag" is written on all the tall large blocks, "bik" on the flat low blocks, "mur" on the tall small blocks and "cev" on the flat small blocks. At the beginning of the experiment all blocks, well mixed as to color and size, are scattered on the table in front of the subject. He is told that there are four kinds of blocks, that each kind has a name and that his task is to find and separate these four kinds. The examiner then turns up one of the blocks, shows and reads its name to the subject and asks him to pick out all blocks which he thinks may belong to the same class. After the subject has done so—selecting, for instance, all blocks of the same color or of the same shape as the sample—the examiner turns up one of the wrongly selected blocks, shows that this is a block of a different kind and encourages the subject to continue trying. After each new attempt another of the wrongly placed blocks is turned up. As the number of the turned blocks increases, the subject, by degrees, obtains a basis for discovering to which characteristics of the blocks the nonsense words refer. He may try to find the difference between the blocks bearing different names or search for the common quality in the blocks bearing the same name. If he succeeds in finding a common factor, the formerly meaningless words are filled with meaning. They come to stand for definite objects (e. g., "lag" for large tall blocks, "bik" for large flat ones), and thus new artificial concepts are built up. As soon as he has formed these concepts, the subject is able to complete within a few seconds the original task of separating the four kinds of blocks indicated by nonsense words. The successful evolving of new concepts thus serves as a means of solving the problem quickly and correctly. The subject who cannot use this tool adequately is considerably handicapped; he will work largely by trial and error, not utilizing the help offered by nonsense words to those who anticipate their potential functions as concepts, i. e., not looking for a common logical principle behind the common designation.

In evaluating the results of the test in each single case one takes into consideration the numerical score, which is based on the time required for the solution and the amount of help given; i. e., the number of blocks turned up by the examiner before the solution is reached. This quantitative score, however is the least important factor. The value of the test lies, first, in the possibility of a detailed qualitative analysis of the procedure of the subject, in which he is comparatively free in spite of the definite task. The setting actually permits observing the processes which lead to concept formation. The subject's manipulation of the blocks reflects nearly every step in his reasoning and in his formation and rejection of hypotheses. At the same time, his comments add to the information. The whole course of the experiment—interpretation of the task, handling of the sample, response to correction, finding the solution—provides a large number of data which may serve as indicators of the degree of conceptual thinking. In analyzing here the results of the test, I shall use data of this type, since the

numerical scores based on time and amount of help have been reported in detail and analyzed elsewhere (Kasanin, J., and Hanfmann, E.: Experimental Study of Concept Formation in Schizophrenia: Quantitative Analysis of Results, *Am. J. Psychiat.* **95**:35-52 [July] 1938). It should be mentioned that the results of this qualitative analysis have also been confirmed by those of the quantitative.

The main results of our investigations were obtained with a group of 50 schizophrenic patients whose performances were compared with those of an equally large group of normal subjects of approximately the same age and educational level serving as a control. The latter group was composed largely of attendants at a state hospital. In addition, we also studied a group of normal persons with college education. Twenty-four patients with organic diseases of the brain—dementia paralytica and arteriosclerosis—served as another control group.

Normal persons performed on the highest level, and patients with organic disease, on the lowest level. The schizophrenic subjects occupied a middle position between the two; yet on the whole their performance approximated more closely that of persons with organic cerebral lesions than that of normal subjects. One of the points which differentiated most clearly between the normal subjects on the one hand, and patients with cerebral lesions and schizophrenia, on the other, was the way in which the solution was reached. Not only did patients take more time and need more help in arriving at the solution; they often reached the end stage of the experiment mechanically, without even partial insight into the reasons for the choice of blocks. In the end all blocks had been turned by the examiner; in other words, the subject never actually solved the problem. This did not occur with normal subjects, but it happened with one third of the schizophrenic patients and with about three fourths of patients with cerebral lesions. Further, a normal subject might reach the solution with only partial insight, but after it was reached and the blocks were organized into four groups he could see that they were organized on the basis of volume; i. e., he was able to grasp the principle of the classification. With patients, whether schizophrenic or suffering from a cerebral lesion, a large number (over one third) were unable to apprehend the general principle as such, in spite of all explanations. When asked how the four groups differed among themselves or what the blocks of the same group had in common, they described and compared the single blocks of the group; it did not occur to them to characterize the total group as such. A given group for them was composed not of all large tall or small flat blocks but rather, for example, of one red block, one round block and one with sharp angles and corners.

From this inability to grasp the principle, to see the arrangement of blocks as representing a concept—in this case, a concept of definite size—follows the last point in which the performance of the normal subjects differed from that of the patients. A normal subject, after having once arrived at the correct solution, was able to repeat the test without errors or hesitation. For him the test meant finding the principle of the classification; once he had found it, he could easily apply it again. That is why the test can be given only once to a normal person. Not so with the patients. About half of them, whether schizophrenic or with a cerebral lesion, were unable to repeat the test immediately after the blocks had been organized correctly in the four groups and then mixed again. These points prove clearly that a large number of patients are unable to grasp the idea of classification and of a particular principle underlying it.

Normal subjects of low educational level, although clearly superior to the patients, by no means always reached the highest level of conceptual approach to the task. It was in fact, only college graduates who, as a group, understood from the beginning the essential nature of the task and tried in a logical way one hypothesis after another, discarding them when the corrections made by the examiner proved them to be false. Among the subjects of the lower educational level who were compared with the patients were some who arrived at the solution in a rather blind, groping way, maintaining that there was no other way to find the blocks of the same name except by turning and looking at the name, or else by mere trial and error. Yet, although approaching the task in this primitive way, the normal subjects eventually arrived at the point where they suddenly

discovered the existence of a principle in the system, whereas a large number of patients could not be brought to that stage. The difference between the normal subjects of different educational levels gives weight to the opinion, which Vigotsky shared with many other investigators that conceptual thinking does not develop fully without a certain amount of formal education.

Thus far, we have discussed the features which schizophrenic patients have in common with those suffering from a cerebral lesion. The question arises whether these two groups show differences? In all points already discussed the patients with cerebral lesions deviated from the normal more than did the schizophrenic patients. If, in addition, one compares step by step the whole process of solving the task, one finds that in practically every point, such as interpretation of the task and utilization of the examiner's help, a larger percentage of patients with cerebral lesions than of schizophrenic patients show impairment in conceptual thinking. On the other hand, the inferior performance of schizophrenic patients occasionally takes on peculiar forms not observed in the other group. When, for instance, the four groups of blocks are designated by the patient as policemen, sick people and working people one had a solution based purely on the physiognomic effect of the material. This kind of solution occurred in our experience only with a few schizophrenic patients and with none of those with cerebral lesions. Another characteristic observed in patients with schizophrenia only was an endless hesitancy and vacillation between one or another of the various aspects of the material. The patient no sooner started to consider color, for example, than his attention was drawn by shape; thus, wavering between the various possibilities, he was unable to follow any method of attacking the problem. The reason for this was his inability to abstract one aspect of the given material while purposely neglecting all others. This inability schizophrenic patients and those with structural lesions have in common; yet the indecision and wavering seem to be more typical of schizophrenic patients. The patient with cerebral disease will be led now by one aspect of the material, now by another, or try to solve the task by trial and error, choosing the blocks purely at random.

Finally, the schizophrenic group is characterized by greater variability. There are among schizophrenic subjects those whose performance is not worse than that of normal persons of the same educational level and also subjects whose performance is extremely poor and cannot be improved by any amount of help and explanation. This great variability suggests that the impairment of conceptual thinking may be prominent in some cases of schizophrenia and not in others.

Summary.—The test for concept formation has shown that reduction in conceptual thinking is an integral part of the schizophrenic picture, or at least of some of its varieties. In extreme cases the defect in schizophrenia may be as pronounced as that in cases of structural disease of the brain, and is essentially of the same nature. Instead of viewing objects as part of some general category, as representatives of a certain class of objects, the patients see them merely as individual objects and are unable therefore to build up, or even to understand, a systematic and logical classification.

DISCUSSION

Dr. A. A. Low: A test that will adequately gage the intellect of the schizophrenic patient has always been desired, but so far tests based on intellectual scores have failed. The invariable result of practically every test has been that normal persons score well, schizophrenic patients less well and patients with organic disease lowest of all. If the Vigotsky tests show nothing else than this they will be of little value. If the test is to be of value it must show more than a mere gradation of scores for the three groups of subjects. I wish to ask about the cooperation of the schizophrenic patients. In dealing with the three groups, one is reasonably certain of this: The normal person cooperates; the person with an organic disease cooperates too well at times; he is too eager and frequently perseverates with the test. If a schizophrenic patient fails in the performance of a test, it is difficult to determine whether failure was due to inability or lack of cooperation.

DR. LLOYD H. ZIEGLER, Wauwatosa, Wis.: Has this test been applied to children? At what point in the life of the child does conceptual disability appear, and when does it begin to disappear?

DR. R. P. MACKAY: Has the test been applied to primitive peoples, and what were the results?

DR. MEYER SOLOMON: In a typical schizophrenic patient, not merely one with a schizoid personality, I think that the essential psychologic difficulty is thought blocking. I doubt whether one is justified in using the term schizophrenia (or dementia praecox) without the presence of thought blocking. It is thought blocking that is responsible for such difficulties in thinking as paucity of thoughts; superficial, uncritical thinking; scattered thinking, and disturbances in association. As a result, the patient feels that he is in a trap situation; he is perplexed, puzzled or cornered, so to speak; he does the best he can in the condition in which he finds himself. Consequently, he drifts into daydreaming, sometimes laughs and sometimes cries and forms delusions and hallucinations in his effort to explain his predicament. This is the cause of his prelogical thinking. It is a condition similar to that which occurs in fatigue states, with lowering of what Janet called "psychologic tension." The patient resorts to primitive behavior reactions, not because they have been inherited, and to childlike reactions, not because they have existed in the unconscious ready to crop out but because there is no other type of thinking or behavior on which he may fall back. It is due to mental fatigue, based on brain fag, as in normal persons. If this is so, as I am inclined to believe, would it not be sufficient to explain the findings mentioned by Dr. Kasanin and Dr. Hanfmann? There are various degrees of regression, depending on the patient; they range from easily reversible types which return to normal readily, on the one hand, to more marked forms, with changes which are apparently irreversible, down to the so-called organic level, on the other.

DR. JACOB KASANIN: I think it is dangerous to generalize about schizophrenia. Some patients are extremely confused, some not. Some patients do well with this test, others poorly. I was able to differentiate a group of patients showing "primary thought disorders," as I choose to call it, with complete inability to deal with the test. Other patients with cases of the paranoid type did unusually well, much better than the others. It was our experience that occasionally patients did better than some of the personnel of the hospital.

I think that the questions of Dr. Ziegler and Dr. Mackay are important. Vigotsky said that conceptual thinking develops at the age of adolescence. I think that it develops in some persons and never in others. These tests are being applied to large groups of children in Iowa City. An expedition was organized, by Luria and Koffka, to try them on primitive peoples. These investigators spent about six months in Central Asia. They found that in places where industrialization was developed the natives showed more tendency to think conceptually. Our observations with regard to cooperation were somewhat different from those of Dr. Low. Our normal subjects, attendants at the hospital, were "scared stiff." They thought they would be discharged if they did not do well on the test. The patients were cooperative. Dr. Hanfmann sat in the room; the patients would come in, look around and walk away, come back, see the test and try to solve it, play with it for a time, walk away and come back. There was much better cooperation with the patients than with normal persons.

DR. EUGENIA HANFMANN: The patients who were preoccupied and absorbed in their thoughts were excluded from the experiment. Our results are based on experiments with patients who were attentive and interested in the test. With regard to the value of the results: The test does more than merely differentiate normal subjects, schizophrenic patients and persons with organic diseases of the brain on the basis of a quantitative measure of achievement. Our conclusions are based on actual observations of what the subjects did while working with the test. These observations show that the patients, even when they are interested and work as hard as normal persons, use methods which are totally different. They never form concepts or try out definite hypotheses, but work in terms of

single blocks. Every one who works with this test will see that it makes possible a study of the mental processes going on in the subject. To describe these qualitative differences is more than merely to say that patients do worse on the test than normal persons.

THE VENTRAL ACCESSORY ABDUCENS NUCLEUS AND ITS RELATION TO FUNCTION OF THE EXTERNAL RECTUS MUSCLE. DR. NORMAN A. LEVY (by invitation).

Foerster and Gagel, as a result of observations that the abducens nucleus does not show the usual retrograde degeneration after section of its peripheral nerve, were led to question whether this nucleus offers an exception to the behavior of other motor nuclei after section of the peripheral nerves or whether it is possible that the abducens nucleus is not the origin of the abducens nerve. This query led to a study of the so-called accessory abducens nucleus of van Gehuchten, which has been described in the entire vertebrate series, including man, but about the function of which little is known. In collaboration with Drs. Wendell Muncie and Tsung-hwa Suh, of the Henry Phipps Psychiatric Clinic, two types of experiments were carried out on cats. Studies of retrograde nuclear degeneration were made after (1) extirpation of the right external rectus muscle and (2) intracranial section of the sixth nerve. Seven specimens were suitable for study in the first series, and 2, in the second. No pathologic changes were present in the principal abducens nuclei, but pyknotic degenerative nuclear changes were consistently present in the ipsilateral accessory abducens nucleus. The results of these experiments seem to afford evidence that the accessory abducens nucleus plays a role in the function of the external rectus muscle and that it is in some way functionally related to the sixth nerve. Further experimentation is necessary to elucidate the exact function of both the accessory and the principal abducens nucleus.

DISCUSSION

DR. REUBEN M. STRONG: I wish to ask whether the so-called trigger function was considered for this nucleus. This involves coordination of the third, fourth and sixth nerves.

DR. NORMAN LEVY: No, it was not. We cut the nerve and observed the change in the nucleus. This is as far as we have gone.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

IRVING PARDEE, M.D., *Chairman of the Section, Presiding*

Joint Meeting, May 10, 1938

PROBABLE TOPOGRAPHIC RELATION OF A SLEEP-REGULATING CENTER. DR. JOSEPH H. GLOBUS.

This paper will be published in full in a later issue of the ARCHIVES.

TREATMENT OF NEUROGENIC MEGACOLON WITH SELECTIVE DRUGS. DR. WALTER O. KLINGMAN.

Since Hirschsprung's original description in 1888 of hypertrophy and dilatation of the colon in children, many possible causes have been advanced, and a variety of therapeutic regimens have been tried. Although neuromuscular imbalance, produced by disturbance in equilibrium between the two parts of the autonomic nervous system supplying the intestine and resulting in paralysis of a segment of the colon, had been proposed as a primary cause, it was not until the experimental

work on sympathectomy by Wade and Royle that a new approach to treatment of megacolon was proposed. After section of the white ramus of the second lumbar root, Royle discovered that relief was obtained in a case of obstinate constipation.

Stimulated by the work of Wade and Royle, Judd and Adson proposed a new theory that congenital megacolon is due to hyperactivity of the sympathetic innervation of the rectum. They therefore proposed and performed lumbar sympathetic ganglionectomy and ramisectomy in treatment of the condition.

In the light of newer knowledge of the physiologic behavior and nerve control of the rectosigmoid region, a rational therapeutic approach with properly selected drugs was attempted. Seven cases were studied. Megacolon was demonstrated by examination with barium sulfate enemas. It was apparent that cases of megacolon fall into two large groups: (1) those of rectosigmoid achalasia, in which one finds failure of the rectosigmoid apparatus to relax, and (2) those in which the rectosigmoid region functions normally but there is failure in motor function above this region.

Various drugs were tested, two of which afforded relief from the obstipation. In the cases of rectosigmoid achalasia in which there was failure of the rectosigmoid apparatus to relax because of lack of proper inhibitory function of the parasympathetic system syntropan, a drug resembling atropine in action, was found to relieve the obstipation. There were 5 cases of this type of disorder in which treatment was successful. In the case of motor weakness of the colon above the rectosigmoid apparatus, but in which the rectosigmoid apparatus functioned normally, prostigmine, a drug resembling physostigmine, was used. One patient was successfully treated. In the cases of rectosigmoid achalasia in which there was hyperactivity of the sympathetic system no drug was found to be of value, and surgical treatment—presacral nerve section—was carried out, with relief from the obstipation.

On the basis of these clinical studies and the experience reported in the literature, a classification of neurogenic megacolon is proposed. 1. Rectosigmoid achalasia caused by (*a*) motor hyperactivity of the sympathetic innervation of the rectosigmoidal apparatus and (*b*) ineffective inhibitory function of the parasympathetic innervation to the rectosigmoid apparatus. 2. Deficient motor function of the innervation of the colon above the rectosigmoid apparatus caused by (*a*) deficient motor parasympathetic function, and (*b*) defective sympathetic motor function.

The results demonstrate an approach to the problem of megacolon on the basis of neurogenic imbalance. A classification of neurogenic disturbances resulting in megacolon with constipation is proposed on the basis of study with barium enemas and trial of appropriate drug therapy. Surgical treatment of neurogenic megacolon is advisable in cases in which there is extreme overactivity of the sympathetic innervation of the rectosigmoid apparatus. Selective drug therapy has proved effective when neurogenic imbalance exists because of faulty inhibitory or motor function of the parasympathetic system.

DISCUSSION

Dr. Edward J. Donovan: I believe that Dr. Klingman has made a real contribution to the management of Hirschsprung's disease, which until a few years ago was difficult to handle by either medical or surgical measures. One is working at a disadvantage in treating this disease, since its cause is unknown and, for that reason, patients must be treated symptomatically. Constipation or obstipation is the most common complaint in all cases; it is not unusual for patients to be without a bowel movement for as long as three weeks. In several of my cases it has been necessary to perform manual removal of impacted feces with the patient under anesthesia.

While in all these cases the colons look alike at operation, I have thought for some time that the conditions do not fall into one group, because of the difference with which they respond to surgical treatment. Dr. Klingman's classification

seems satisfactory; by dividing the cases into two groups one may explain why in some instances the condition does not respond to sympathectomy. Development of surgical procedures on the sympathetic system has been a great advance in the successful surgical treatment of Hirschsprung's disease. It is a great improvement over the surgical measures used earlier for this condition. Resection of large segments of the colon was often an operation of such magnitude that it was too much for a child to stand and often did not help the condition.

There are two types of operation on the sympathetic system, both of which have been successful in the treatment of Hirschsprung's disease. The first is resection of the presacral and inferior mesenteric nerves; the second includes removal of the second, third and fourth sympathetic ganglia on the left side, together with resection of the presacral nerve. In 5 of a series of 9 cases I performed presacral neurectomy and did both neurectomy and ganglionectomy in 4. In 6 cases the results were excellent, and the patients have been followed for from one to six years. In 2 cases the results were classified as 85 per cent successful and would easily have been 100 per cent if the patients had received attention at home. In the ninth case the result was classified as a 50 per cent success; the daily enema is now much more efficacious than before operation, and the condition is otherwise unchanged.

There are several drawbacks to surgical intervention in cases of megacolon; perhaps the most important is that it has been stated that resection of the presacral nerve paralyzes the ejaculatory ducts in the male. Another drawback is the difficulty of performing this type of a surgical procedure on an infant. Then, there is the usual risk which goes with any abdominal operation. If Dr. Klingman continues to be as successful as he has been so far, surgical intervention, with its drawbacks, will not be necessary in these cases. One of the greatest advantages of medical treatment is that it may be started earlier in life, when surgical measures cannot be carried out easily.

I show a few lantern slides depicting large segments of the colon removed in 2 cases for relief from Hirschsprung's disease. In both cases there was a recurrence of the symptoms in less than a year after the operation. I removed the presacral nerve in 1 of these cases ten years after the colon had been resected. This operation was successful. In the second case resection of the presacral nerve with removal of the second, third and fourth sympathetic ganglia on the left side was equally successful.

DR. H. A. RILEY: I am not entirely clear, after hearing Dr. Klingman's presentation, whether he believes Hirschsprung's disease is due to overactivity of the parasympathetic system or underactivity of the sympathetic system—whether there may be an imbalance in action of either system, with reciprocal disturbance in function of the opposite system. I wish also to ask Dr. Klingman what is his routine in determining which component—whether overactivity or underactivity—of the sympathetic or of the parasympathetic system is the cause in the particular instance of megacolon.

DR. WALTER O. KLINGMAN: I think that Dr. Riley's first statement is correct; megacolon may occur from overactivity of the sympathetic system, resulting in localized constriction; I have termed this rectosigmoid achalasia, or failure to relax. The opposite condition of deficient functioning of the parasympathetic system results in failure of proper inhibitory function of the circular fibers. Cooperating, coordinating interaction is necessary. It must be complicated in order that all these elements may function perfectly.

In reply to Dr. Riley's second question as to how I determine into which group a case belongs: When there is good function of the rectosigmoid apparatus I believe that the condition lies in faulty motor action above the region of the junction of the sigmoid and the rectum. In these cases, when the barium reaches that point good emptying will occur. When the rectosigmoid apparatus did not function I used the trial and error method, treating the patients first with benzedrine

sulfate and then with syntropan; the therapeutic results enabled me to classify the defective mechanism, for syntropan reacts only on the parasympathetic system, whereas benzedrine is likely to reduce tonus of the circular fibers activated by the sympathetic system.

PSYCHOPATHOLOGIC ASPECTS OF EMOTIONAL DIVORCE. DR. PHILIP R. LEHRMAN.

(This paper will appear in full in the January 1939 issue of the *Psychoanalytic Review*).

The states of mind and the accompanying emotional distress which precede legal action for divorce are best described as "emotional divorce." When legal divorce is obtained and neurotic or psychotic illness appears in the open, it is indicated that the marital difficulties are the symptoms of a more basic neurotic or psychotic illness. Such patients are generally not suitable for regular psychoanalysis, but are amenable to psychotherapy by the analyst.

The women patients in the series in which I made observations had many features in common and may be presented as a composite portrait: that of a woman in the fourth decade of life, with children who required little physical care and, in fact, protested against any continuation of the role of dependency which the woman, out of her own needs, tried to maintain. When there were no children, the husband was the recipient of attentions which were more suitable to a child than to a man. Also, there was recent loss of the father, either by death or by removal to a distant city, with a striking lack of inadequacy of mourning. Pathologic character changes, as well as manifestations of hostility and revenge, appeared; the latter arose out of a feeling of insecurity, based on ideas of having been neglected and deprived of something fundamental by the husband. Transient paranoid trends took the form of acute jealousy, and symptoms of melancholia with talkativeness were evident. There were attempts at reparation by becoming easily drawn into idealized, abstract social movements. A feeling of "being independent" was experienced.

An attempt to evaluate the various factors which bring about the crisis in the marital difficulties of the woman takes into account the insecurity which, at a certain period in her life, seems to be caused by a series of exogenous and endogenous deprivations. The appearance of secondary male characteristics and pseudomasculine values and actions (drive for money, "Doll-House" and surprise situations) is discussed. Usurpation of the husband's work and role is associated with envy of the penis. Castration is magically maneuvered by "running away" and litigious activities. Eventually, there is degradation of the feminine role by masochism and revival of other unresolved infantile conflicts.

The psychopathologic picture presented indicated the following general conclusions: First, though it is usual to regard marital difficulties as the concern of the state and the law, modern medicine, with its concern for the total personality, must regard this disturbance of interhuman relationships as a symptom of disease. Second, legal divorce is a pseudoremedy for a self-diagnosed condition. The legal adviser is incapable of evaluating disturbances which arise from physiologic and psychologic sources. The client for divorce is analogous to a patient who, because of a pain in the back, decides for herself that her kidney is at fault. The lawyer behaves like an untrained surgeon who, without subjecting her to a careful, scientific examination, agrees with her pseudodiagnosis and proceeds to extirpate the kidney. Because special disciplines have always been concerned with what have been regarded as special and separate problems, in matters of legal divorce scientific medicine has shown no concern, nor has it been consulted. Especially by those who are interested in psychologic medicine, physical symptoms (such as backache or dysmenorrhea) and the social symptom of divorce are looked on not as independent, detached categories but as different aspects of one nosologic entity, which arise from the same psychopathologic source.

DISCUSSION

DR. CLARENCE P. OBERNDORF: I regret that Dr. Lehrman was compelled by illness not to be present tonight, and I appreciate Dr. Klein's sympathetic presentation of the paper. I wish Dr. Lehrman could have been here, because I should be interested in his comments on the discussion.

The problems of divorce must necessarily begin with the institution of marriage. One must inquire why persons want to marry and why practically all stations of society, all types of people, civilized and semibarbarous, have forms of marriage. I think the answer to this question touches the kernel of Dr. Lehrman's presentation. It is this: At the back of every person's mind is a vestige of the early desire in childhood to possess, to cherish or to be associated with another person in the situation which seemed so enviable to him as a child, namely, to be with another person as his father or mother were together in his childhood. This hypothesis leads to the Oedipus situation, which is considered to be the nuclear conflict in most neurotic manifestations. Certainly, in marital complications it comes up frequently. The Oedipus complex also accounts for significant kaleidoscopic changes after marriage. One patient said to me seriously, shortly after the minister had performed the ceremony and his troubles with his wife began: "Doctor, I cannot understand that girl at all. Before we were married she was calling me up two or three times a day, and now she is calling me down every few minutes."

I do not wish to discuss in detail how the Oedipus situation reacts in the negative way after a person has acquired a mate. Suffice it that certain prohibitions against incest inherent in the Oedipus situation begin to operate unconsciously and often may make the partner somewhat distasteful.

I think that Dr. Lehrman put himself in the position of inviting trouble when he constructed a composite portrait of the woman who wishes a divorce. He is in a predicament similar to that of many colleagues who have exhibited pictures in the current art exposition and have presented nothing as complicated as a composite portrait, but a single person. Each observer stands before it and becomes eloquent concerning the points which he does not like, seldom mentioning those of which he approves.

So, in Dr. Lehrman's composite portrait there are many things which seem to contradict my own experience. One of the weaknesses, perhaps, in Dr. Lehrman's presentation is that he described only the feminine psychologic attitude associated with divorce. After all, marriage is a merging of interests—psychologic, physical and emotional—of two persons, but Dr. Lehrman has confined his portrait to the reactions which the woman passes through at a certain period.

In 1930, before a meeting of the American Neurological Association, I presented a paper, entitled "The Psychoanalytic Factors in Divorce," and followed it in 1931, before the American Psychiatric Association, in Toronto, Canada, with another, entitled "Psychoanalysis of Married Couples." I have refrained from publishing either paper because I wished to accumulate further data. During twenty-five years I have had the opportunity of analyzing each member of 9 married couples. Often the analyses of the couples were conducted simultaneously—a rather dangerous procedure, perhaps—but it seems to have worked out satisfactorily. In a review of these cases, which I have finally collected, I did not find often the characteristics of the woman which Dr. Lehrman mentioned in his composite portrait. For instance, the woman was not necessarily the favored sibling. The favored sibling may be the favorite not of both parents but of only one parent; which parent favors the child is an important factor. Second, there was no loss of a parent immediately preceding the difficulties for which the dissatisfied couples came. Most of them were young, and the women were not undergoing the physiologic changes of the premenopause. Third, their children were not beyond the need of the mother's care. One woman was pregnant at the time; another had a baby a year old. While Dr. Lehrman's composite picture may correspond with his own experience, it does not seem to fit in with the data in the cases of the 9 couples which I investigated at length.

The causes usually assigned for marital difficulties and divorce were not present in this series. First, one often hears that one of the reasons that people divorce each other is that they have no children. Most of these couples had children. A second reason often assigned is disparity in age between husband and wife. In most of the cases there was a normal disparity in years—a difference of three or four years between husband and wife. Only in 1 case was the husband twelve years older. In 1 case the wife was a year or two older than the husband, but he was not aware of it. Third, religious differences were not present. Most of the couples were of the same religion. In 1 case there was a Protestant-Catholic marriage, in which the religious difference played a slight role. Furthermore, the question of economic status, which Dr. Lehrman has emphasized, did not prove a serious factor. Finally, I come to infidelity. Dr. Lehrman mentioned that women seeking a divorce seldom have the courage to be unfaithful. In my cases there had been infidelities by several of the women and by many of the men.

The most potent causes for marital infelicity are emotional, and these I have grouped under three headings. The first is the Oedipus situation, which involves overattachment to one parent or the other. This Oedipus situation has many ramifications. Any of the familiar instinct derivatives, such as oral, urethral or anal impulses, which may enter into the development of the Oedipus situation may be emphasized as the most important, according to the opinion of the analyst, but essentially the crux is unconscious incest.

The second factor in divorce is emotional immaturity. This is also closely related with the Oedipus situation. The child who is overattached to the parent usually remains emotionally immature. When such an emotionally underdeveloped persons assumes that the new husband or wife will treat him with the same indulgence as the parent, he immediately encounters disappointment.

The third important factor is the degree of homosexuality unconsciously operative in each person. Some women have considerable difficulty in accepting the feminine role, and a few men never attain a maximum of masculinity. Discord is particularly likely to result when such a woman attempts to assert her masculinity, particularly in embarrassing situations. Then the feminine man withdraws and may attempt to seek a solution of the situation by divorce. Similarly, a woman may attempt to seek the divorce as a way out of a feeling of insecurity, due to her husband's weakness.

Finally, an important point raised by Dr. Lehrman is that there has been, and probably will be, a change in the adjustment of marital controversy. Most of the men and women in this group of 9 couples expressed the belief that divorce was a poor solution of their difficulties. They both recognized that something inherently wrong in their makeup was responsible.

When I take as the basis for the study of causes for divorce persons who are distinctly pathologic, I can say only that in such cases the fundamental elements stand out prominently, whereas in the so-called normal relationships the same causes may be operative, but not as distinctly. For years the family physician, the clergyman and the lawyer have attempted to adjudicate these difficulties. Most of these men are not well oriented in scientific knowledge of the underlying causes. It seems that the time is ripe, and has been ripening for the past twenty years, when a more intelligent solution of these difficulties will be effected, because both parties often realize that, while divorce is perhaps a way out, it is not the true solution for the underlying psychologic problems which bothered each person prior to marriage.

DR. LOUIS CASAMAJOR: Divorce is a definite part of modern life. In the last hundred years in this country conditions have increasingly arisen to make divorce possible. In modern life there seems to be a definite tendency toward more divorces. The law is catching up with it, encumbered by its complicated verbiage and its various excuses which can be used to save feelings. The churches are lagging and catching up much more slowly, as they have caught up with all social movements in their slow fashion. One hundred years ago in this country there

were few states which allowed divorce. Now there is only one state in the Union that does not permit divorce on some grounds. These grounds are often ridiculous, if one looks at them from a purely human point of view. In most states the main, and sometimes the only, ground is infidelity, but others have gone beyond that; so one has the various legal verbiages and reasons that are merely excuses and rationalizations for the desire to terminate a marriage. Cruelty and the latest, vaguest and most meaningless of all, mental incompatibility, serve as an excuse to break the relation of two persons who no longer desire to live together.

If one wishes to understand the problem of divorce, if it is really important in modern life, and I am not sure that it is, one must go back of these various excuses and legal subterfuges and find out why people do not want to live together. For men the problem is relatively simple. The large majority of men who secure a divorce, and this includes the men who induce their wives to secure the divorce from them because it is the more gentlemanly thing, do so because they wish to marry some one else—a frank, simple and fairly honest procedure. The number of women who secure divorces for that reason is relatively small. I have been interested in observing women who want divorces, and I have wondered what it is all about. I think many of them do not know what they want, and Dr. Lehrman has given me a totally new idea about the matter. Relatively few women secure divorces because they want to marry again. There are a number of homosexual women who obtain divorces because they married without knowing what they were doing and, having found out what marriage was like, decided to be rid of it. This class, I think, makes up rather a small number. There is another group, however, which has interested me for years—a group of women who want divorce mainly on such grounds as mental cruelty and mental incompatibility. I have talked with a number of them. There seem to be much talk and a minimum of ideas. I have the impression in talking with them that everything they say clouds the issue and obscures the meaning. Dr. Lehrman, I think, is speaking of this group, women who want divorce not for the divorce itself, because many of them are thoroughly dissatisfied as soon as they obtain it. These women up to the time of divorce are fairly well adjusted. Through self pity, a large amount of talk and much sympathy from women of their acquaintance they lead fairly satisfactory lives. Dr. Lehrman mentions this group and states that they are constantly finding excuses for putting off going to the lawyer to start the proceedings. Divorce lawyers tell me that they will start the proceedings and call them off; if the lawyer tries to force them to carry through the suit, they frequently discharge him. After a while they return to the state in which they were before and seek another lawyer. Obviously, this desire for divorce is not the same as the desire one finds in most men. These women are looking for something, but divorce is not what they think they want. Divorce in these cases is entirely an emotional matter. It is merely a symptom of a neurosis, and when they succeed in obtaining the divorce they frequently find it necessary to acquire new symptoms in order to keep alive the neurosis. They seldom secure from divorce the happiness and adjustment they are seeking. I think Dr. Lehrman struck a true note in describing these mechanisms as infantile—the desire of the women to return to a parent-child situation. It is the sort of thing one sees in many neurotic persons—merely a symptom which in this complicated society has taken on definite legal aspects. I have had little experience with these persons, although I have seen not a few; I have often wondered how many there are whose difficulties are symptoms of a generalized neurosis.

Dr. George H. Hyslop: Dr. Lehrman has used his clinical material in a study of a certain social relationship. Several years ago Hamilton, in a study of approximately 100 married couples, in apparently successful marriages, found that about 50 per cent of these persons had had at least one attachment to a person of the opposite sex during married life. This "attachment" varied from simply "thinking about things" up to the point at which there was actual infidelity. These persons, however, had the ability, whether inborn or acquired as the result of experience,

to keep a balance and stick to reality and to maintain not merely the amenities in their relation but with a feeling of contentment toward the partner. I have seen a number of persons whose marriage careers "went on the rocks." Viewing the problem from a standpoint other than presented, I think these persons fall into two categories: first, those who could never be fit mates and, second, those who, as the result of misfortune or unfortunate choice, or perhaps misjudgment of the other partner, find themselves married to a complete misfit; one half of the couple is all right; the other is not. I think that if, from the long view and the biologic standpoint, matrimony is an institution which makes for the most efficient development of the next generation there is something to be said (and I am a heathen) for the Roman Catholic prohibition of divorce. If the majority of couples who "are on the rocks" have serious personality defects, if one can keep them from marrying again, the next generation is better off. Whether that is a feasible point of view today I shall not argue, but it is something to think about. I have not yet dealt with a person, man or woman, for whom marital discord was a prominent issue who had a personal background making for solid citizenship. Some of them may have had abilities in certain directions, but they were not adjustable as far as matrimony was concerned. When one thinks of the various reasons for maladjustment, another matter enters into the problem; that is, whether these excuses are the only matters to be considered. There are certain rules of conduct which, if followed, keep people away from the shoals and rocks of life. In my reading, not only in psychiatry but in law, and in sociologic discussions insufficient emphasis is placed on the duty of the person to conform to well established rules of conduct. Most persons understand and try to live up to the fact that two and two make four. There are too many excuses made for those who persist in trying to make two and two equal seven.

DR. SIMON ROTHENBERG, Brooklyn: I wish to comment on the statement by Dr. Casamajor that those who seek divorce do not know what they want. I shall go further and say that the fundamental trouble seems to be in their not having known what they wanted when they married. Much of the difficulty with the divorce problem, to my mind, is with the problem of mating. What does any one know about choosing a mate for matrimony? As it is now, mating is somewhat haphazard. Most often it is fortuitous; the idea that marriages are made in heaven is outmoded. There is need for psychology to develop more knowledge of the problem of mating. What are the facts concerning successful mating? Which character types are fit and which are unfit for marriage? I think a study of the subject from the point of view of psychoanalytic experience will in time give the real knowledge that is being sought to determine the true causes leading to divorce.

DR. S. BERNARD WORTIS: From the data presented in the discussion, it seems to me that perhaps the difficulty lies in the fact that Dr. Lehrman has tried to overcodify a problem that does not as yet allow of such treatment. Dr. Oberndorf's experience with 9 married couples apparently gives evidence that the dynamic factors which he thought important are entirely different from those which Dr. Lehrman found important in his cases; I believe that both are right. It is foolish to attempt to oversimplify the problem of divorce when so many factors contribute to the personality of any individual person. When two persons try to unite in a home, the personality factors are further interactive, and one can be certain that no simple equation will explain all divorce problems. However, Dr. Oberndorf's grouping is a laudable attempt.

Another factor should be emphasized. Although patients come to the physician and discover that their reasons for desiring a divorce are due either to an unresolved Oedipus attachment or to unsatisfied libidinal tendencies, many of them, after they have learned this, proceed to secure the divorce just the same! In many cases, the mere understanding of a personality problem, whether it be put in psychoanalytic language, in psychiatric language or in the common sense language of everyday life, does not remake the personality structure. Analytic

understanding is no panacea. Dr. Lehrman said many of these persons need help from the physician. I dare say that many such persons come to the psychiatrist and that not a few obtain real help.

The economic factor is important. The Catholic or the Protestant family who is poor and has to live in simple circumstances cannot afford the wisdom of the psychiatrist or the psychoanalyst and must depend on that of the parish priest or of a friend; I suspect that the proportion of divorces among such persons is smaller than that in families who have better economic surroundings. Often, despite gross maladjustment in personality, the wife will not want to divorce her husband because he represents to her an economic stability which she could not obtain without him. Even if one puts into the language of the layman, the analyst or the psychiatrist the differences in personality which may cause divorce, there will be left a certain proportion of "maladjusted" persons who will not be divorced under any circumstances. All divorce may be looked on as a problem in personality maladjustment, and I think any attempt to oversimplify the problem is not justified by the facts. I have no objection to the person who wishes to use psychoanalytic technic or understanding of these problems. Perhaps the best marriage counselor is the person who has some knowledge of analysis by personal experience. However, I doubt if the management of divorce problems is more effective when expressed in such language. Symbolization can be a potent motivating force at many levels, and the psychiatrist should utilize all levels rather than voluntarily restrict himself to one methodology. Language, thought and behavior depend on constitutional, psychologic, environmental, social and anthropologic factors, and any attempt to see or interpret all human behavior solely in any one of these categories is near sighted, or perhaps an evidence of mental tubular vision!

Dr. Israel S. Wechsler: It seems to me that if Dr. Lehrman would use simpler terms and regard the psychopathologic condition as "one aspect of divorce" and not as "the cause of divorce" he would be closer to the truth. Two problems are generally ignored or confused in discussions of divorce. These are love and marriage. They are not at all synonymous. They may exist separately or be dovetailed. Love may last an hour, and vary intensely; it may last weeks or months or years. It depends entirely on the individual makeup, on constitution or character. Marriage, on the other hand, is a social problem in which society is enormously interested. It is no accident that society frowns on divorce and condones infidelity. Marriage is a social institution, and it has many other functions than the gratification of love. Successful marriage implies an enduring state, a stability for years. All hope to make love and marriage synonymous, and it is a blessing for a man and woman to go through married life full of love, but there can be fairly successful marriages without volcanic or intense love. They may not be the best or the happiest marriages, but they are by far the most frequent. Sexual love often survives only a temporary period of married life. Indeed, much of married life, particularly if it extends to advanced years, must go without that love which in youth is so essential to life. To speak of divorce merely from the psychoanalytic point of view and to overlook the social and economic implications or the question of children and of religion or morals which marriage entails are to view the problem from one angle only. It seems to me that much of the discussion centering around the problem fails of its purpose because many factors are left out, particularly because the fundamental cleavage that has existed and continues to exist between the individual aspect of love and the social aspect of marriage is not fully grasped. Unless adult persons realize this and the need of dovetailing them or not, as the case may be, and do not fly into separation the moment desire cannot be gratified, the marriage cannot endure. Granted that the psychoanalytic, especially the sexual, aspect of marriage is tremendously important, it is only one side, perhaps not the most important, of the problem of marriage as a social institution.

DR. LEWIS J. DOSHAY: I agree with Dr. Wechsler that there are more ways of approaching the divorce problem than from the psychoanalytic angle. The psychoanalyst may approach it purely from the standpoint of the Oedipus complex, but, as Dr. Oberndorf said, one secures from a painting what is in one's own background and what one is looking for. One may use also the sociologic approach. There are other ways of interpreting the problem than purely by the Oedipus complex. No doubt the endocrinologist would approach it from the angle of glandular disturbances, sterility, impotence or frigidity in the males. The phychiatrist would approach it from the point of view of constitutional factors. Sometimes one sees constitutionally inferior persons who are incompatible because of inability to assume the usual social and economic responsibilities.

Fixed habits of individual persons also help to contribute to divorce, and these, I believe, have little to do with the Oedipus situation or the psychoanalytic interpretation of unconscious mechanisms. There are habits of drunkenness in a man which may or may not have psychoanalytic determinants. Because of bad habits, a man may not be prepared for responsibility; he may not want actually to return to the mother fixation situation at all, but, because of an immature status, may want merely to return to his friends, to play cards or to keep late hours. Bad habits often contribute to divorce, and purely psychoanalytic mechanisms should not be considered as explaining the problem.

DR. IRVING PARDEE: Not being a psychoanalyst, I beg to venture on that field slightly, for it seems to me that the element of the ego enters strongly into the divorce situation. When two persons marry, one of the problems which is presented to them is that of which shall dominate the household. This is an important factor. Often, the struggle in the household goes on for two, three, five, ten or more years. If the struggle for dominance is settled, divorce will not take place. If the struggle continues and one or the other is not willing to be subjugated, the issue eventually results either in an emotional divorce with infidelity or in a legal divorce. Sadism and masochism also enter into the picture, depending on the individual case. The problem of divorce at present is a question of the mental attitude of the population. Divorce is easy to obtain today as compared with thirty years ago; many marriages are entered into with the belief that divorces can be readily obtained. Therefore marriage is not entered into as a firm and durable union, and as soon as conflicts develop husband and wife rush to the divorce court. Many years ago divorce was unthought of. Consequently, marriages were adjusted, and the husband and wife, in spite of difficulties and neuroses, found some way to live on, reasonably content.

DR. SIDNEY KLEIN: Dr. Lehrman was fully aware of the fact that in the period of thirty or forty minutes assigned for the paper it was impossible to deal with a theme to which he believed he could devote thirty evenings or more. I think that a paper like this is of value only as it flashes before the physician, the lawyer and the intelligent layman the thought that when there is a question of divorce, brought by husband or wife, neurotic illness should be thought of. That in itself is significant. The other details are of an extremely technical nature, which the trained psychiatrist is in a position to recognize, given the opportunity to examine the patient. One thing is necessary: The divorce seeker should realize that something is wrong with him. Such persons may possess an otherwise symptomless neurosis, that is, a "neurotic character," and may have no insight.

I personally never like to feel myself in a position in which I should assume the right or dare to make rules regarding marriage or divorce. As a clinician, I should be interested in studying material and endeavoring to discover what is going on in that material from a psychopathologic standpoint. Dr. Lehrman has reported on the results of his experience. Many of these persons may not be subjects for analysis, just as all abdominal pains are not amenable to lapar-

otomy, but with insight into the material the therapeutist is better able to deal with the problem. I am sure, from my knowledge of Dr. Lehrman's work, that he never tells a patient that she has a father or a mother fixation. That is not the nature of analytic work. The patient lives through a definite infantile experience and is then herself in a position to tell what she has.

With regard to adjustment of personalities to marriage, some persons do that for themselves. I have a close friend who was a passive sort of fellow through his college days; he married a girl who "wore the pants," and they are getting along excellently; he is highly successful, owing to the fact that they are mated properly. Another friend intruded when a woman was badly beaten by her husband; he received a rebuff and was told to mind his own business. Some like it that way. One knows that in marital life a successful relationship, or successful coitus, is sometimes impossible without a sadomasochistic experience between the two. One cannot formulate personalities, with their particular instinctual dispositions and organizations. What one can do is to open the eyes of the intelligent physician, lawyer and layman to the fact that when there is a cry for divorce the psychiatrist should have a look.

PHILADELPHIA NEUROLOGICAL SOCIETY

JOSEPH C. YASKIN, M.D., *President, in the Chair*

Regular Meeting, May 27, 1938

DEAFNESS DUE TO MUMPS: REPORT OF A CASE. DR. RICHARD L. MASLAND (by invitation).

A white boy aged 14 had been in normal health until Aug. 5, 1938. The illness began in the afternoon with severe headache, dizziness and vomiting. The temperature was 101.2 F. That evening the patient became deaf in the right ear. The next morning the temperature was normal, and he felt well. He had no further illness, but loss of hearing in the right ear persisted.

The history was otherwise without significance except that at the time of the illness there was an epidemic of mumps in the community and the patient's sister had had typical parotitis five days before the onset of his illness. The patient did not show any glandular involvement.

Neurologic examination in October 1938 gave normal results except for the eighth nerve. Otologic examination showed no evidence of otitis. The tonsils were slightly large and cryptic. The results of a Bárány test were as follows: The right vertical semicircular canals failed to respond after caloric stimulation for three minutes. The right horizontal canal gave a fair response. The left vestibular apparatus gave no response after caloric stimulation for three minutes. An audiometer showed complete loss of serviceable hearing for all frequencies in the right ear, the left ear being normal. (Determination was made with masking.)

The Wassermann reaction of the blood, roentgenograms of the head and the eyegrounds and visual fields were essentially normal.

There was no change in the patient's status after that time except the audiometric findings. Between February and May 1938 there was definite improvement of about 20 decibels in the right ear, bringing the level of hearing up to that of hearing by bone conduction.

In spite of the absence of glandular involvement, the patient's symptoms were thought to be due to the virus of mumps, for the following reasons: 1. The onset of deafness was characteristic of that occurring during mumps. The sudden onset (usually from within one week before to one week after the appearance of parotitis), the short course and the diffuse, random involvement of cochlear and vestibular divisions were typical of that condition. 2. The illness did not con-

form to the usual picture of other syndromes causing deafness. 3. The diagnosis of mumps need not depend on the presence of glandular swelling. It is a generalized infection. The spinal fluid shows abnormality in 80 per cent of cases. During an epidemic at Camp Lee, during the World War, Howard observed 9 cases of encephalomyelitis associated with mumps. In only 6 of these was there glandular enlargement, the neurologic condition in the other 3 being the only evidence of the disease.

It is believed that the difficulty in making a positive diagnosis in sporadic cases has prevented the recognition of the disease in many instances and that the prevalence of the condition is greater than is generally appreciated.

DISCUSSION

DR. OSCAR V. BATSON: There is little to add. In November the patient reported hearing only three of the eight octave frequencies for which he was examined. The intensity of these three indicated a loss of hearing of approximately 80 sensation units (decibels). Examination in February showed slight improvement, but at the time this was supposed to be due to observational error. A poor prognosis was given. The mother was advised to see that the boy had a seat in school that would allow him to depend on his good ear. In the most recent examination, a few days ago, the patient's hearing was well within the range of intensity of the audiometer; the hearing loss averaged about 40 sensation units (decibels). This was obviously a perceptive lesion. The recovery was not expected. Possibly this experience should cause one to be less pessimistic about this type of deafness.

DR. J. C. YASKIN: Are there any statistical data on the frequency of occurrence of deafness in cases of mumps?

DR. RICHARD L. MASLAND: The reports are contradictory. Hubbard, in 1915, reported that in from 3 to 5 per cent of cases of deafness in institutions the cause was mumps. That only about 100 cases have been reported in the literature is probably due to lack of interest. Thus, Radin, in reporting 5,765 cases in a concentration camp during the World War, said that all grades of deafness were present, but made no further comment.

DR. W. L. LONG: Would you hazard a guess as to the nature of the process in this case?

DR. RICHARD L. MASLAND: Voss, in 1931, discussed that question. He considered, first, the possibility that the process is an ascending infection from the parotid gland, but this is ruled out by the fact that deafness may occur when there is orchitis and not parotitis. Second, it was thought that the disease is a meningitic process. In favor of this is the fact that other cranial nerves are often affected and that the spinal fluid is frequently involved in cases of "uncomplicated" mumps parotitis. The third possibility is that the disease is acute labyrinthitis. The picture appears to differ, however, from that in the usual case of acute labyrinthitis.

MULTIPLE NEURITIS PROBABLY DUE TO SULFANILAMIDE: REPORT OF A CASE. DRS. A. M. ORNSTEEN and WILLIAM FURST (by invitation).

(This paper appeared in full in the Dec. 3, 1938, issue of *The Journal of the American Medical Association,* page 2103).

Except for optic neuritis, the literature contains no report of a case of neuritis in man resulting from sulfanilamide. Our patient was admitted to the neurologic service of the Philadelphia General Hospital on Feb. 11, 1938, because of weakness in the hips and legs, of one month's duration. After a gonococcic infection in September 1937, he was given approximately 2,000 grains (130 Gm.) of sulfanilamide during a period of one month, in spite of which there developed gonorrheal arthritis. He responded well to four hours of fever therapy in the Kettering

hypertherm. One month later gait became cumbersome, and the hips and legs grew increasingly weaker. This was associated with patchy numbness and paresthesias in the distal portions of the lower extremities.

Pertinent physical findings were: marked weakness in abduction of the thighs, tenderness on compression of the hamstring muscles and calves of both legs, weakness on dorsiflexion of the left foot against slight resistance, waddling gait suggestive of progressive muscular dystrophy, elicitation of knee jerks only on reenforcement, absence of the achilles reflex bilaterally and diminution of sensitivity to pinpoint below the middle third of the legs. The results of laboratory studies were essentially within normal limits. Sulfanilamide was not detected in the blood.

With rest in bed and brewers' yeast, muscular tenderness subsided and the knee jerks returned. Sensory impairment disappeared, but motor weakness was still evident. Before further studies could be completed, the patient left the hospital, believing that he was almost cured.

Experiments on mice by Bliss and Long, on dogs by Custer and his associates and on rabbits and cats by Hawkins demonstrated that sulfanilamide is toxic to the central and peripheral nervous system, producing ataxia, spastic paralysis, loss of reflexes, blindness and symptoms resembling decerebrate rigidity. It is probable, then, that sulfanilamide was responsible for the neuritic condition in this patient.

DISCUSSION

DR. R. S. WIGTON: If the condition was really neuritis due to sulfanilamide, this case is of great interest not only because of the wide use of the drug but because of the interest that has been expressed in the relation of all cases of peripheral neuritis to vitamin B.

Two cases of peripheral neuritis due to compounds related to sulfanilamide were observed at the University Hospital. One patient received dimethyldisulfanilamide, and the other, sulfanilylsulfanilamide. Both patients received moderate doses for two weeks. After an interval, both experienced pain for two days. Subsequently, both had marked weakness of flexion in the toes and ankles. About a week later one complained of weakness in grip, particularly of the adductor muscles of the thumb. Reaction of degeneration in these muscles was incomplete. The polar formula was reversed. In both cases the condition is now of about two months' duration and there has been some improvement, but both patients are left with considerable disability, so that there is no doubt as to the severity of the neuritis.

In 1 case heavy doses of vitamin B, from 30 to 50 mg. daily, were given intravenously until 250 mg. had been administered in sixteen days. There was no improvement except that two hours after the first injection the patient insisted that his grip was normal. Dynamometric readings showed an increase of from 10 to 15 points, which is well beyond the range of error that may be expected. Strength in the feet did not improve.

I think that this presentation is significant because when persons are ill with the various conditions for which sulfanilamide is given neurologic sequelae may be overlooked. In 1 of the cases the patient was under observation in the ward and no effects were noticed until an intern saw that the patient, while carrying trays, had a slight foot drop. The patient had hardly noticed it himself.

DR. J. C. YASKIN: If the neuritis developed in January, is there any doubt in regard to the interval between the time of administration of the agent and the development of the symptoms?

DR. WILLIAM FURST: That is the stumbling block in this case. I cannot believe that the neuritis was due to anything but the drug, since one surely would have heard more in the past of gonorrhea as a cause of neuritis. A case in which neuritis was due to exposure in the Kettering hypertherm has as yet not

been reported. However, experimental evidence supports the contention that sulfanilamide may be toxic to the nervous system in various species of animals. Dr. R. P. Custer, at the Philadelphia General Hospital, has been carrying on extensive experiments along this line with dogs and has shown definitely (and his opinion has been confirmed by Dr. Helena Riggs, who has pathologic specimens of the brains and spinal cords of his animals) that the drug is not toxic to the bone marrow but affects the capillaries, producing edema that is reversible. Perhaps one can correlate the interval of one month with this experimental evidence.

CARBON DISULFIDE POISONING WITH A REPORT OF SIX CASES. DRS. SAMUEL T. GORDY and MAX TRUMPER (by invitation).

(This article appeared in full in the May 7, 1938, issue of *The Journal of the American Medical Association,* page 1543).

With the rapid growth of the rayon industry, a health hazard has reappeared —carbon disulfide poisoning. The United States is one of the largest rayon-manufacturing countries in the world, having produced 290,000,000 pounds (145,000,000 Kg.) in 1936. Of the twenty-five rayon factories with 50,000 employees now operating in this country, nineteen are viscose plants using carbon disulfide. For every 3 pounds (1.3 Kg.) of rayon produced 1 pound (0.5 Kg.) of carbon disulfide must be used. In 1936 more than 33,000,000 pounds (16,500,000 Kg.) of carbon disulfide was consumed by one large viscose corporation.

Foreign journals contain reports of many hundreds of cases of poisoning from carbon disulfide in viscose and rubber plants; yet in the United States this form of poisoning has received little attention in medical journals. For some reason, the subject has been shrouded in mystery, and to our knowledge only 5 reports have been made by American authors: Peterson, in 1892; Heath, in 1902; Jump and Cruice, in 1904; Francine, in 1905, and Hamilton, in 1925. We reported 6 cases and made examinations in 20 more. With the application of the new compensation laws for occupational diseases in many of the states, more will be heard of this insidious poison.

Poisoning with carbon disulfide for the most part results from the industrial use of this substance. It occurs from inhalation of the vapors when, for some reason, ventilation is not properly carried out or a breakdown in mechanical ventilation occurs. This substance is a good fat solvent and finds industrial use in the defatting of hides and wool, in the extraction of sulfur for the purification of illuminating gas, in the cold vulcanization of rubber and, more recently, in the production of artificial silk (viscose method). Intoxication may also occur by absorption through the skin. In contact locally with the skin, it produces a sensation of burning, followed by anesthesia. Prolonged contact, through its refrigerant action, results in second and third degree burns, with blistering and local neuritis.

For the sake of convenience, one may differentiate three forms of poisoning: acute, subacute and chronic, but in many individual cases or groups of cases manifestations may partake of all or any of the three.

In the purely acute forms the symptoms resemble those of other toxic narcotics, such as chloroform, ether and carbon tetrachloride, consisting, in rapid order, of severe headache, nausea, vomiting, muscular weakness, profound coma and death. In the less severe forms which are not immediately fatal acute psychoses are especially prominent, notably, confusion, restlessness, yelling, weeping and laughing, maniacal behavior and epileptiform convulsions.

The subacute and chronic forms have a protean symptomatology, with emphasis on neuropsychiatric disorders. These may be divided into three groups: the somatic, the neurologic and the psychic. In most cases there is a combination of two or three groups.

Somatic Symptoms.—Various types of cardiac disturbances, such as tachycardia, bradycardia, stenocardia and angina pectoris, are encountered. Gastro-

intestinal disorders are especially prominent, and may include obstinate constipation or intractable diarrhea, gaseous distention and anorexia, gastrointestinal ulceration and great weakness. There also occur simple anemia and loss of weight. The general asthenia which occurs frequently even after recovery in cases of the acute form is directly related to damage to the adrenal glands. A case resembling Addison's disease, with pigmentation of the skin and subsequent death, following exposure to carbon bisulfide vapors in a research laboratory in Switzerland, has been reported. Respiratory symptoms occur, with asthmatic episodes. Disturbances of libido and potentia are noteworthy.

Neurologic Symptoms.—Headache, nausea, vertigo, vomiting (of central type) and various visual disturbances are most frequent. The last are of special significance. There are dimness of vision, disturbance of color perception, transient amblyopia (which may last twelve, twenty-four or thirty-six hours), retrobulbar neuritis, various types of scotoma, pupillary changes and corneal anesthesia. There may be alterations of tendon and superficial reflexes, paresthesias, dyesthesias and anesthesias. Muscular weakness or definitive paralysis, muscular fibrillations or tremors, bladder disturbance, central and peripheral palsies and polyneuritis may occur. Involvement of the basal ganglia may give a picture characterized by parkinsonian facies, tremor and rigidity, cerebellar components and other evidence of extrapyramidal disorder. Headache, visual disturbances and vomiting may simulate a picture of tumor of the brain. Hemiplegic and monoplegic syndromes occur, with chorea, athetoid movements and epileptiform seizures.

Psychic Symptoms.—These symptoms are rich in variety; frequently bizarre alterations in conduct, of labile nature, are encountered. There are tipsiness and loss of inhibition, causeless laughter and crying, unmotivated rage and allied symptoms, which have frequently been mislabeled hysteria (by Charcot and Pierre Marie) or neurasthenia. In addition, definitive psychotic syndromes occur, the most frequent being of manic-depressive type, with excitement, flight of ideas and increased psychomotor activity or episodes of depression, stupor and ideas of reference alternating with the manic state. Fleeting or persistent delusions of persecution or sinfulness may occur, together with dreams of a horrifying character. Prolonged stupor or catatonic excitement may vary the picture. In some cases there is simple mental deterioration, which is usually of bad prognostic import. Fugues, petit mal episodes and periods of amnesia occur. The clinical picture may resemble various neurologic, neurosomatic or direct psychiatric disorders. A case of the Korsakoff syndrome complicating a great variety of chronic neurologic signs, together with complete autopsy observations (with modern neuropathologic technic), has been reported by Masazo. He observed destruction and chromatolysis of the ganglion cells in the cerebral cortex, especially the motor area, in the cerebellum (especially the Purkinje cells) and in the basal ganglia. Aside from the disappearance of myelin from the medullary sheaths, the meninges and brain showed no gross edema. There were fatty changes in the heart and liver. These changes in a chronic condition of thirteen years' duration explain and substantiate similar results in experiments on animals which have been carried out by various workers since the earliest reports by Delpach, in France, in the 1860's. It should be borne in mind that there is usually a combination of visceral, nervous and psychic symptoms, with each group represented in most cases. Such a combination is suggestive of a disorder with disseminated loci of injury resulting from repeated inhalations of a lipoid solvent. Lipoids are the common denominator of the structure and function of neural tissue—ganglion cells, axons, dendrites, myelin and neurilemma. It follows that lipophilic toxic agents are likely to inflict simultaneous, consecutive or heterogeneous lesions wherever lipoids are located. These may be reversible (recoverable) or irreversible (permanent or chronic). In cases of acute, subacute or chronic poisoning by lipophilic toxins, among which carbon disulfide is preeminent, the clinical manifestations will therefore present a rich variety. Indi-

vidual case reports and the more recent statistical groupings serve to illuminate and reemphasize the clinical and experimental studies as well as the neurologic and psychiatric observations of Delpech, the able French hygienist who first reported 24 cases of the disorder before the French Academy of Medicine, in 1863.

The mode of action of carbon disulfide is clear; it is lipotrophic—hence neurotoxic. This is to be inferred a priori from its physicochemical properties. It is demonstrated by pathologic material in experimental animals and in man. There can be no doubt that many of the respiratory, cardiac and gastrointestinal symptoms as well as the vasomotor and endocrinopathic disturbances encountered among the sequelae to acute poisoning and in the course of chronic carbon disulfide poisoning can be ascribed to disorganization within the strategic centers of the body economy, namely, the respiratory center and the neurovegetative regulators in the diencephalon and medulla.

We may classify the 6 cases which we studied as 3 cases of the so-called acute and 3 of the chronic form of this disorder. In all 6 cases there was a relative paucity of neurologic signs. In 2 there was corneal anesthesia. The visual disturbances were noteworthy; 2 patients complained of what may be termed "wavy vision"; 2 had retrobulbar neuritis, and 1 had lilliputian and brobdingnagian hallucinations (or illusions). As far as we are aware, "wavy vision" and hallucinations of this type have hitherto not been described in cases of carbon disulfide poisoning.

Especially noteworthy was the periodic or cyclic character of psychotic episodes with sequelae, in 4 of the cases of a variety of paresthetic or hallucinatory phenomena. Chronic fatigue and asthenia were present in 2 cases, amnesic features in 2 and progressive mental deterioration with memory defects in 1. Four patients had diminution or loss of libido. All are industrial invalids.

DISCUSSION

DR. F. H. LEWY: The speaker deserves the thanks of the society for having again aroused public and medical interest with respect to the industrial hazards of carbon disulfide. He pointed out that in the literature in this country there are a number of scattered descriptions of the disease, but there has been, as far as I know, no real understanding of the neurologic complications of the problem until now. The practical importance is obvious; during the last three weeks my associates and I had 3 cases of carbon disulfide poisoning at the Hospital of the University of Pennsylvania.

The severity of the symptoms depends on the degree of acuteness of the poisoning. It is dreadful to realize in what percentage of workers in the plants the pyramidal and extrapyramidal symptoms are present; in the great group which we have examined, there were, besides the 3 at the hospital, over 60 persons having definite disturbances of the peripheral nervous system, and even more in whom the corneal reflex was decreased, or even lost.

An interesting point is that the hazard is not confined to those working in the plant but extends also to their families. This is in contrast to the condition in England and Germany, where regulations have been enforced for more than thirty-five years. The workers in the United States are permitted to leave the factory in their working clothes and so transport carbon disulfide into their homes. Obviously, in that way the health of a whole family is at stake.

DR. MAX TRUMPER: From the toxicologic point of view the quantity of carbon disulfide that will produce pathologic changes in the various portions of the nervous system is microscopic. The exact amount has been estimated by European authorities to be as low as 5 mg. Dr. Gordy and I are now on record as stating that carbon disulfide should not exceed 10 parts per million in the air which the worker has to breathe. The United States is well known for its efficient industries. In many large viscose plants one finds that the productive capacity has been stepped up by as much as 75 per cent. This means that the worker must be very active. The increased activity doubles the internal exposure to carbon disulfide, because

the volume of respiration per minute must keep pace with the high speed of production. Unless the viscose industries make careful daily analyses of the air in various portions of the working rooms, workers will continue to be seriously poisoned. Continual vigilance is necessary to make early repairs on machinery from which there is an escape of this highly toxic gas.

In my studies on breathing (with 400 adults) I found that many persons who heretofore had been considered to have an idiosyncrasy to a toxic gas had in reality merely breathed more of the gas than their fellow workers. This may have resulted from their working harder or from a greater internal exposure due to high ventilation volume of the lungs.

One point I wish to add: Though I have no proof, I am inclined to believe that carbon disulfide is a germ plasm poison. Injury to children of workers would be due to damage to the germ plasm and not to the absorption of the gas from working clothes.

DR. N. C. NORCROSS: I wish to ask on what basis the optic nerves were studied in the cases and whether there was any determination of the amount of carbon disulfide in the blood stream and urine.

DR. W. L. LONG: I advise caution about including in the symptomatology a great many manifestations which may not belong there. The paucity of the literature is such that, although I am willing to admit that the disease attacks many parts of the nervous system, I should hesitate to include cases of loss of weight with secondary anemia or of neurasthenia. It seems to me that one should limit oneself to what the literature states.

Dr. J. W. MCCONNELL: Will Dr. Gordy tell something about the findings in the blood in these cases? I am impressed with the similarity between some of his cases and cases of benzene poisoning I have seen recently. There is a close similarity, and I should like to know what is the difference in the blood picture. In benzene poisoning the outstanding feature is the tremendous reduction in white blood cells, which in 1 instance fell to 1,250.

DR. J. C. YASKIN: Are there any chemical or laboratory tests that tell with certainty that one is dealing with this particular form of poisoning?

DR. SAMUEL T. GORDY: With regard to findings in the blood and urine: The literature describes certain odors and changes in the urine in cases of acute poisoning, but none of the cases we have seen were those of the acute phase. With respect to the blood: I do not believe that carbon disulfide can be regarded as a hemolytic agent. It is simply transported by the blood stream to do its damage elsewhere, although it may and does cause simple anemia. An Italian investigator reported changes in the blood sedimentation rate. An increase in the sedimentation rate is such a general phenomenon, associated with so many other conditions, that it is not specific for carbon disulfide poisoning. However, carbon disulfide, being a lipoid solvent, may alter the suspension stability of the red cells, in addition to its other effects.

In answer to the question by Dr. Long about some of the symptoms which appear to be vague: I may say that that is precisely the reason for the gathering of the material for these case reports. There may be a paucity of case reports in this country, but there certainly is none abroad. Examination of these reports illustrates the rich variety of the "imponderable" symptoms. When a patient describes the anxiety associated with a sense of impending doom it is no more significant that a Babinski sign, for such subjective complaints occur with many other conditions. The mere fact that there is not in all cases a neat regimentation of identical symptoms is not proof that the symptoms recorded do not arise from the poisoning.

Charcot and Pierre Marie ascribed the bizarre symptomatology to hysteria, but since the occurrence of epidemic encephalitis and its sequelae there has been a vast change in neurologic philosophy, especially concerning hysteria.

With reference to Dr. McConnell's comment concerning the similarity of the symptoms to those he has encountered in cases of benzene poisoning: I may add that it is true that carbon disulfide and benzene poisoning have many symptoms in common. They are both lipoid solvents, but benzene has, in addition, hemolytic properties and a toxic effect on the bone marrow. The metabolism of benzene is also different. The fact that benzene is a cyclic compound and that in cases of poisoning the liver attempts the role of detoxication complicates the picture and must also be considered. As far as I am aware, carbon disulfide is more toxic, other things being equal; yet the side effects of benzene—the hemolytic and, more especially, the profound depressor effects on hematopoiesis—make the clinical picture of benzene poisoning more variegated than that of carbon disulfide, especially in the aid which the laboratory may afford in diagnosis.

COMPRESSION OF THE SPINAL CORD IN OSTEITIS DEFORMANS (PAGET'S DISEASE) OF THE VERTEBRAE. DRS. GABRIEL A. SCHWARZ and SAMUEL REBACK, M.D., New York (by invitation).

In 1877 Sir James Paget published a clinical and pathologic study of a deforming type of bone disease which he called "osteitis deformans." The chief characteristic of this disease is the haphazard proliferation of soft new bone and destruction of the old bone. Deformity results from the abundance of new bone as well as from the distortion of weakened bone. It must be obvious that the central nervous system, as it is entirely encased with bone, must often be involved in this disease. Thus, in the literature one finds cases recorded in which disturbance of the brain masses and of the cranial nerves are complications. Compression of the spinal cord or of the spinal nerves, however, has been reported in only 10 cases; yet vertebral involvement by this disease process is not infrequent. Some authors explain this discrepancy on the basis of the softness and slowness of development of the abnormal bone.

In the 10 cases reported in the literature, the average age at which the patients were first seen because of the neurologic disturbances was 56 years. All were men. All but 2 of the patients showed slow, gradual progression of the symptoms over the average period of one year. In 2 cases the neurologic symptoms occurred suddenly. In most of the cases there was paraplegia of spastic type, with a sensory level in the thoracic region and bladder and rectal disturbances. Four of the patients were subjected to decompressive laminectomy and recovered all or most of the lost functions. One patient died soon after operation. In 1 case in which no operation was performed, sudden initial quadriplegia developed, with partial recovery and a residual Brown-Séquard syndrome. The sensory level and root pains in this case correlated well with the picture of a fracture dislocation of the diseased fourth cervical vertebra.

At the Neurological Institute of New York we studied 9 cases of compression of the spinal cord resulting from Paget's disease of the vertebrae. Two of these cases occurred in women. The average age was 58. In all but 1 case gradual onset and slow progression of the neurologic symptoms occurred. The average duration of the illness before the patient was seen was about one year. In 1 case there was sudden development of paraplegia during the slow onset of neurologic disturbances. All the patients presented weakness or paralysis of both lower extremities, with sensory levels in the thoracic region. One patient was operated on in 1921 and remained well for a period of ten or eleven years, when recurrence of the symptoms again brought her to the hospital. Another patient was operated on in 1935 and, after a year of slow recovery, has remained well to date. The third patient on whom operation was performed died a few hours after laminectomy because of a cardiac complication. There was nothing characteristic in the clinical features of the cases to establish the diagnosis; this rested entirely on roentgenologic findings.

Compression of the spinal cord in cases of Paget's disease of the vertebrae may result (1) from narrowing of the vertebral lumen by proliferating bone, either diffusely or in exostoses, or (2) by sudden collapse, dislocation and/or fracture of the diseased vertebral body. The former causes a slowly developing picture, while the latter produces one of sudden onset. It is suggested that decompressive laminectomy is of distinct value in cases of Paget's disease of the vertebrae with compression of the spinal cord, providing certain features are properly evaluated. First, the extent of the actual compression must be determined by injection of iodized poppyseed oil or a myelogram, for it is not advisable to perform too extensive a laminectomy in the vertebral structures that have already been weakened by disease. Second, because osteitis deformans occurs in early senility and because of the associated generalized arteriosclerosis, the patients present a greater operative risk, and precautions must be taken particularly to prevent too much stress from falling on the cardiovascular system. Technical difficulties due to the massive bone and the extreme vascularity of the new osseous tissue are also to be considered in such an operation. It is of further interest to point out that in most of our cases and of those recorded in the literature the chief point of involvement of the spinal cord was the thoracic region. This is probably due to the fact that this region presents the smallest difference between the size of the spinal cord and the volume of the vertebral space.

In conclusion, we believe that although osteitis deformans frequently involves the vertebrae, compression of the spinal cord as a complication of the disease at this site must be unusual. In 4 cases reported in the literature and in 2 of our cases the patients recovered lost function after decompressive laminectomy. It is urged that laminectomy is definitely indicated in cases of Paget's disease of the vertebral column in which the symptoms and signs of involvement can be definitely proved to be the result of compression of the cord by the deformed, pathologic bone.

DISCUSSION

DR. P. J. HODES: Since much of the responsibility for the diagnosis of Paget's disease is dependent on roentgenographic examination, it may be well to point out several pitfalls in the roentgenographic diagnosis of this disease. I have seen many patients in whom it was impossible to differentiate Paget's disease from metastatic carcinoma of the prostate until postmortem studies were obtained. Hodgkin's disease and the other lymphoblastomatous diseases are also known to produce changes easily confused with osteitis deformans. One wonders, therefore, whether in questionable cases a therapeutic test by means of irradiation may not be indicated. Certainly, it can do no harm in osteitis deformans, and it might save a patient with an unusual type of malignant growth the ordeal of a major operation. I do not believe, however, that it would be wise to continue with a therapeutic test if the patient's neurologic symptoms rapidly became more severe.

Dr. Irvin Stein, of the orthopedic department of the Hospital of the University of Pennsylvania, has treated patients with Paget's disease medically, with encouraging results. One wonders how much good this type of treatment will do patients with symptoms referable to the cord. In view of the fact that osteitis deformans may undergo malignant degeneration and eventually produce damage to the cord, one wonders whether it is not wise to examine for metastasis the lungs of patients being prepared for operation. Certainly, if pulmonary metastases are well established one would hesitate to perform laminectomy.

Dr. Schwarz said nothing about the subsequent care of these patients. Is any attempt made by means of orthopedic appliances to prevent deformities of the spine following operation?

DR. B. J. ALPERS: In the cases in which there was narrowing of the vertebral canal were any other bony openings involved? I had always thought that the spinal cord is involved by direct compression or by vascular involvement. It seems to me that there must be vascular involvement, in view of the high degree of arteriosclerosis usually present in these cases. Is the recovery always complete after laminectomy?

DR. MAX ABRAMOVITZ: Was there any roentgenographic change in the long bones of the body in your cases or in the cases reported in the literature?

DR. N. C. NORCROSS: In considering an operation, what thought is taken of the state in which the bones are at the time of operation?

DR. GABRIEL A. SCHWARZ: The diagnosis by means of roentgenographic examination is, of course, rather definite, but sometimes, as suggested by these cases, it may be doubtful. However, in our cases we were certain of the diagnosis for several reasons: There was involvement of other bones in almost all cases. Furthermore, chemical studies, particularly those made for us by Dr. Alexander B. Gutman, who has written a great deal on this subject, confirmed the diagnoses. Finally, in several of our patients who were subjected to operation or on whom autopsy was performed, there were definite histologic evidences of Paget's disease. We think, therefore, that although the other possibilities mentioned by Dr. Hodes should be considered, our cases are definitely those of Paget's disease.

As to postoperative treatment, unfortunately, limited experience in 2 cases in which operation was performed does not permit me to say how valuable it would be. One of our patients, although showing definite improvement since operation, is given a brace at present. It is advisable to do so.

How the compression occurs is not clear. Wyllie, in his report of cases (*Brain* 46:336, 1923), had a picture of a vertebra that he had removed in a case of Paget's disease in a museum in London. It showed diffuse narrowing, an actual reduction in the size of the lumen; so I assume that in these cases there is slow compression. Whether or not the primary action is on the vessels that supply the cord I am not certain.

It is true that arteriosclerosis occurs frequently in Paget's disease, and there have been reported cases of paraplegia without block in which it was believed that no laminectomy should be done. In 1 of our cases in which autopsy was performed, we observed that the spinal cord was compressed. This has also been seen at operation. Furthermore, in sectioning the spinal cord, we saw degeneration of the white matter at the periphery of the cord.

The patients, when they came to us, did not present the typical picture that Paget described—the simian appearance with a huge head. It was only by means of the roentgenogram that changes were seen in the vertebrae; when the sacrum and skull were roentgenographed, lesions were also found there.

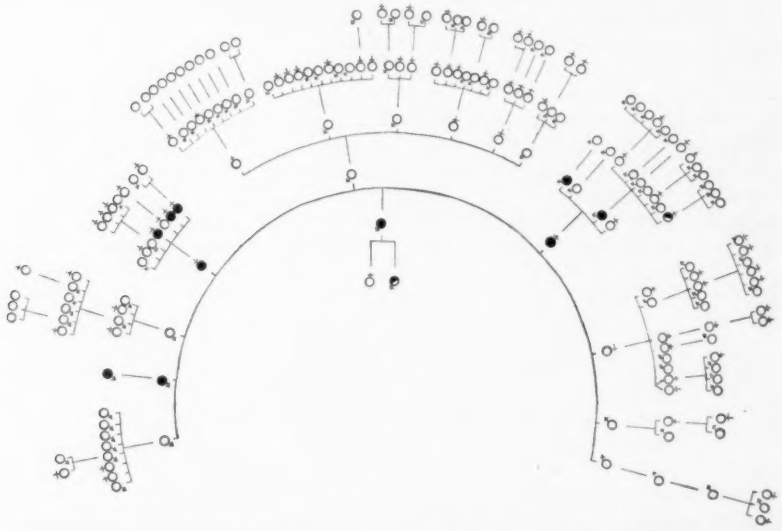
As far as the two stages of osteitis deformans which Dr. Norcross mentioned are concerned, we have never considered them in operating. The two stages are usually combined. There is just as much hardening as softening, and we make no allowance for this.

HEREDOFAMILIAL DEGENERATION OF THE CEREBELLUM (CLINICAL AND GENEALOGIC REPORT ON A FAMILY). DRS. ANNA P. KLEMMER, ROLAND N. KLEMMER and FRANK ALLEMAN, Lancaster, Pa.

CASE 1.—E. S., aged 52, was under observation for three years. For the past six years she has had progressive difficulty in walking and, coincidentally, urinary incontinence. Three years ago she began to have a steady pain in the right upper extremity. This persisted for about one year and did not recur. She stated that prior to these symptoms she had never had "a hard spell of sickness" in her life. Her weight had never exceeded the present one of 96 pounds (43.5 Kg.). The asynergia which began in the lower extremities gradually progressed to the upper limbs and at the time of the report affected nearly all voluntary movements. The right arm was weaker and more unsteady than the left. The irregular movements were accentuated by active motion, or even by the attempt to maintain static equilibrium, as shown by the nodding tremor of the head when the patient sat erect. There was increased resistance to passive manipulation of the extremities. The grip of the relatively normal left hand, although slowly applied, became surprisingly strong and was then slowly relaxed. Speech was slow, jerky and monotonous. She had considerable difficulty in formulating words. Her husband

stated: "When water catches in her throat she coughs as if she would strangle." There was some generalized muscular atrophy, apparently due to disuse. Ocular examination revealed slight ptosis but no nystagmus. The pupillary reactions, visual fields and visual acuity were normal. The deep reflexes were slightly exaggerated; there was no clonus, however, and the plantar reflexes were normal on both sides. Sensibility to touch, pain and temperature was preserved. Vibration sense was slightly impaired in the upper extremities and greatly diminished in the lower. The sense of position of the great toes was lost. On testing for Romberg's sign we found marked swaying, but practically no difference in situation whether the eyes were open or closed. The liver had been enlarged, firm and practically invariable in size for at least three years. It extended about 9 cm. below the costal margin. Mentality was perfectly preserved.

CASE 2.—A. W., the sister of the patient in case 1, was under our observation for thirteen years before her death, which occurred at the age of 55. With few exceptions the findings in her case were similar to those in the preceding case.



Genealogic record of a family in which cases of heredofamilial degeneration of the cerebellum appear.

She had no pain. Difficulty in walking was of ten years' duration, with grossly staggering gait for eight years, dysphagia for three years and dysarthria for five years. Speech was jerky, extremely explosive and accompanied by pronounced facial grimaces. Although the patient stated that she weighed 170 pounds (77.1 Kg.) at the age of 30, she finally became emaciated and had generalized muscular atrophy. The two sides of the body were equally affected.

Eight other members of the family were reported by a number of observers to have almost identical symptoms, but were not examined personally. Two other relatives had suggestive symptoms, but the available information was insufficient to classify them properly.

The disease begins in the thirties or early forties with ataxic gait; it progresses slowly without remissions to difficulty in control of the arms, jerky and explosive speech, dysphagia and finally death in the forties or early fifties. Death is practically never due to the disease itself, but is usually the result of an intercurrent infection. The affected men become fathers, and the women bear children even when the disease is far advanced. There is no mental deterioration.

Two members of the family died in the second decade of so-called encephalitis, but the diagnosis was not confirmed. Two other members had dementia praecox; another has petit mal.

Conclusions.—The cases of 2 sisters, who obviously had some form of cerebellar degeneration, are reported. One died, without necropsy. Genealogic study (chart) showed that the same disease affected at least 8, and probably 10 additional members of the family. The disease was apparently transmitted as a dominant mendelian characteristic and was not sex linked. The cases of other neuropsychiatric disease in the members not affected by cerebellar degeneration suggest that there was a tendency to abiotrophy, that is, a poorly endowed central nervous system. The clinical findings were almost identical with those in the cases described by Gordon Holmes (A Form of Familial Degeneration of the Cerebellum, *Brain* 30:466-489, 1907), except that he was unable to discover any hereditary characteristic in the family he studied.

DISCUSSION

DR. J. W. MCCONNELL: I have been trying to think of the cases of this disease in the Philadelphia General Hospital at the moment. There are the red-headed twins and, I think, 4 or 5 other patients. They have not been studied genealogically, except possibly the twins. Besides these 2 patients, there have been perhaps 7 or 8 others, who either have died or are still distributed about at several places. To me, this presentation is of tremendous interest.

DR. J. C. YASKIN: Have any autopsies been made in these cases?

DR. ANNA KLEMMER: In connection with Dr. McConnell's remarks, I may explain that this family is scattered from Panama to Boston and from Oklahoma to Pennsylvania. Most of them still reside in Lancaster County. As I stated, they all came from Germany.

Unfortunately, we have had no autopsies. We hope that in the future we may be able to report on such observations. Unfortunately, also, there are still a great number of the family who may have this disease who are still too young to show any signs of it at present.

RELATION OF THE HISTOLOGIC TO THE CLINICAL FEATURES OF ABSCESS OF THE BRAIN. DR. BERNARD J. ALPERS.

Twenty-seven cases of abscess of the brain were analyzed histologically in order to determine how and when encapsulation takes place and to determine, if possible, the relation of the bacteriologic findings in the abscess to its encapsulation. It was observed, roughly speaking, that the older the infection the greater the likelihood of encapsulation. However, this rule must not be interpreted too rigidly, since capsules may be seen early in some cases of abscess and not at a similar stage of development in others. This variability is the result of differences in the nature of the invading organism and the resistance of the host. Abscess capsules have been observed as early as ten days after the onset of infection, and in the present series, as early as six days. A review of the cases shows that in the early stages there was no capsule at three days, a beginning capsule at six days, no capsule at ten days and definitely greater evidence of capsule formation from fourteen to twenty-one days. In cases in which the duration was from three to six weeks, there was a good capsule in every instance. In cases in which the duration was more than six weeks the results were variable. In 1 case in which the duration was two months there was a poorly formed capsule, and in another in which it was two and a half months there was no capsule whatever. In still another abscess of eleven months' duration encapsulation was poor. On the other hand, in 11 other cases in which the duration varied from two to eleven months good encapsulation had occurred. It may be interesting to point out incidentally that in all the cases of traumatic origin encapsulation was always complete and was usually heavy.

The conclusions to be drawn from this experience are: 1. In general, the older the abscess formation in the brain the greater the likelihood of encapsulation. It does not follow from this, however, that every abscess as it becomes older and more chronic becomes more heavily, or even adequately, encapsulated. Exceptions to this rule have been cited from our own experience and from that of others. A case of abscess of eleven months' duration in which there was no question concerning the presence of cerebral infection during the entire period and in which no capsule was observed makes it possible to say only that in most cases time will result in the development of a capsule, but that this is not an invariable experience. 2. It does not follow, furthermore, that as an abscess becomes older the capsule becomes heavier. The present study and the experience of others indicate clearly that abscesses of short duration (twenty-one days) may be heavily encapsulated, while older abscesses may possess inadequate capsules. The reason for this is not clear. It is obvious, however, that a traumatic abscess almost always possesses a heavy capsule because of the participation of the dura and pia mater in the formation of the capsule. The density of the capsule is dependent also on the bacterial population of the abscess, as in the case of formation of the capsule. The clinical significance of these factors will be considered subsequently.

Much remains to be clarified concerning the relation of bacteria to the formation of encapsulated abscesses, but this much seems clear: Anaerobic bacteria are conducive to poor capsule formation; conversely, aerobic bacteria produce good capsules; mixed infections on the whole are not conducive to development of good capsules. It is well to know how to measure the virulence of the invading organism and the resistance of the host in making one's decision as to whether capsule formation has taken place or will occur. It has been stated that time is the most important element in the formation of an abscess capsule. Hence it is reasonable to assume that in cases of acute abscess the longer one waits before operation the better the chance of encountering a walled-off process. This is true in most cases, but it is not invariably so, for there are well known instances in which there was no, or very inadequate, encapsulation after several months. In most cases, if the situation is not too acute, it is advisable to wait at least three, and preferably four, weeks for encapsulation, and hence for operation. This is not always possible, because in some cases the onset is so acute and the situation so desperate that immediate intervention seems necessary. It is doubtful whether operation will do more than satisfy anxious relatives in such cases, because histologically only encephalitis is present; the abscess has not yet formed. On the other hand, that this is not invariably the case is shown by occasional recovery from a very acute condition after operation, before encapsulation has occurred. In such acute forms it is probably better first to remove the focus of infection in the sinuses or the mastoid and follow this with a period of watchful waiting, in the hope that the type of organism and the resistance of the patient will permit encapsulation to take place.

It is desirable to point out also that an encapsulated abscess is not by any means a quiescent abscess. Within the abscess cavity may be virulent bacteria which, if permitted to escape into the meninges, may produce fatal meningitis. Practically all abscesses contain bacteria. Only occasionally is a sterile abscess encountered. This is intimately associated with the problem of encephalitis around the abscess in some cases. Even in the case of old abscesses one sometimes observes active encephalitis in the tissue around the capsule. In our series this was invariably a sign of a very active abscess. It is desirable to know whether such encephalitis is present in certain cases, in order to be prepared for it in the operative approach. Thus far, however, no signs have been found which could be regarded as characteristic of the encephalitic reaction.

Conclusions.—1. Twenty-seven cases of abscess of the brain were studied histologically and bacteriologically. 2. The histologic appearance of the abscesses is described, especially with reference to formation of the capsule. 3. Time, the type

of organism and the resistance of the host are the most important factors in development of the capsule. 4. The optimum time for capsule formation is from three to four weeks.

DISCUSSION

DR. R. A. GROFF: I think Dr. Alpers is to be complimented on this excellent work. It is extremely important from the standpoint of treatment of abscesses of the brain. Especially important is the fact that it takes at least from three to four weeks for encapsulation to take place. This has been confirmed in clinical material observed by Dr. F. C. Grant. When the abscess was allowed to remain from three to four weeks before operation the patient did much better than when operation was performed before that time.

More important is the point that a number of the abscesses do not encapsulate adequately or at all. Dr. Yaskin recently described at a meeting of this society a group of 4 cases. In 1 instance there was no encapsulation, and the history was of only about one week's duration. The situation was so desperate that operation was performed immediately on the patient's admission to the hospital. The abscess was partially drained, and adhesions were allowed to form between the dura and the opening to the abscess cavity. About two days later the abscess was drained by means of a rubber tube. Dr. Yaskin and I were fortunate in being able to watch the formation of the capsule; approximately from ten days to two weeks after the abscess had been opened and the tube inserted, we saw a wall forming on the side adjacent to the tube. This is an interesting phenomenon because it shows that even acute abscesses, if treated conservatively by partial draining and partial decompression, may encapsulate.

Another point that is important in connection with Dr. Alpers' studies is the degree of encapsulation. Recently, Dr. de Martel suggested complete enucleation; unfortunately, the capsule ruptured at the time the attempt was made to remove the abscess in toto. However, the outcome was fortunate, and the man is making a complete recovery. I hesitate, therefore, to subscribe to Dr. de Martel's ideas with regard to complete enucleation of abscesses of the brain, in view of the fact that not all abscesses encapsulate adequately.

In closing: There are two problems in connection with abscess of the brain. The first is encapsulation, and the second is intracranial pressure. Certainly, if intracranial pressure becomes dangerous to the patient's life, it should be relieved first by either partial removal of pus from the abscess or decompression, which will reduce the pressure until encapsulation can take place.

DR. J. C. YASKIN: The first question in any case of suspected abscess of the brain is this: Is there an abscess? I challenge the neurosurgeons to prove that the question is not important. Most of the time they are not sure that there is an abscess, even in cases of contributing diseases of the ear, nose and throat. I am sure that Dr. Alpers has a great deal more in his paper about encephalitis than he has given. The question is extremely important, especially on the operating table. Dr. Alpers' contribution is important in many ways. It is a study of 27 cases by one man, whose competence one needs not doubt.

DR. BERNARD ALPERS: I wish to remark on one of Dr. Groff's points, that some abscesses do not encapsulate. That is true. Some abscesses run their entire course without encapsulation. Probably the most important aspect of the problem is concerned with the virulence of the organism and its action on the host in relation to formation of the capsule. If one could determine what type of organism is more likely to induce formation of a capsule and what type of person is more likely to acquire resistance, one would go a long way toward understanding when and why abscesses form.

The important clinical problem, it seems to me, outside the question whether an abscess of the brain is present, is this: What signs in the whole constellation indicate waiting, and what signs indicate that one must not wait? This question is still unanswered, because there are so many questions that are still unsolved.

Obituaries

FREDERICK TILNEY, M.D.
1875–1938

On Aug. 7, 1938, Frederick Tilney died at his summer home in Oyster Bay, L. I. He had borne a year of illness with fortitude and with a realization that his work in this life was almost ended. He left behind him a host of sincere friends and admirers.

Dr. Tilney was born in Brooklyn on June 4, 1875. He received his early education at the Brooklyn Polytechnic Institute and then entered Yale University, from which he was graduated in 1897. After several years of newspaper work, he studied medicine in the Long Island College of Medicine and received the degree of doctor of medicine from that institution in 1903. In the same year he married Miss Camilla Hurley, who, with one son, survives him. After serving as an intern in the Kings County Hospital, he began the practice of general medicine in his native city of Brooklyn. From the beginning of his professional career, Dr. Tilney was interested in the nervous system, and this interest was stimulated by his preceptor and lifelong friend William Browning.

In 1906, in the anatomic laboratory of George S. Huntington at the College of Physicians and Surgeons, he began his researches on the hypophysis cerebri, and from that time his interest in the comparative anatomy and morphology of the central nervous system never waned. In 1914 he was appointed associate professor of neurology, and in 1915, professor of neurology at the Columbia University College of Physicians and Surgeons. Although an increasing private practice made large demands on his time and energy, he devoted himself to the development of the department of neurology at the medical school and spent much time in the laboratory. For many years he was to be found at his anatomic work not only on working days but evenings, Sundays and holidays.

Through Dr. Tilney's efforts and enthusiasm, the department of neurology at the medical school was made to include neuroanatomy and neuropathology, and the teaching of all these subjects was done by members of the staff of the department of neurology. At the same time, the outpatient department in the Vanderbilt Clinic was built up, and for many years Dr. Tilney personally worked in the outpatient clinic.

In 1919 he was appointed to a neurologic service at the Neurological Institute of New York; although he seldom spent much time in the public wards, he organized a department of great efficiency, and was able to attract to the institute the best workers in neurology and allied branches in New York city.

Meanwhile, in order to satisfy the demands of his private practice and to spend as much time as possible in his laboratory, he had moved from Brooklyn to Manhattan.

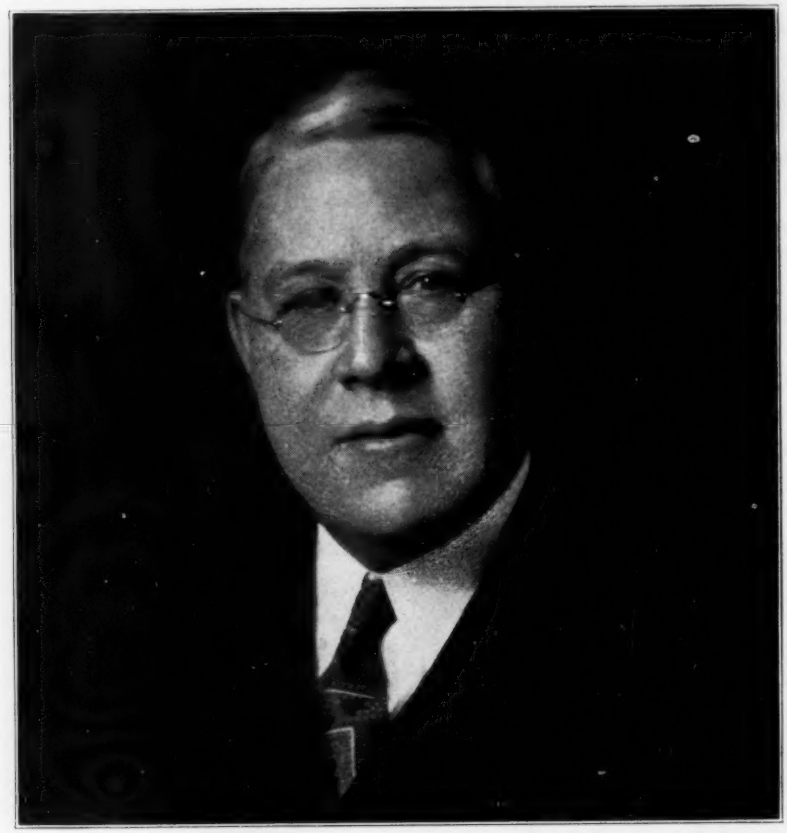
In 1929, largely through his efforts, the Neurological Institute had merged with the department of neurology at Columbia University and had moved up to a new building at the Columbia-Presbyterian Hospital Medical Center. With great enthusiasm he joined his colleagues in building up the new institution, and he was always in the front line in efforts to extend the usefulness and reputation of the organization.

In 1924 he had an attack of cerebral thrombosis with right hemiplegia and aphasia. He fully recovered his speech, learned to walk with hardly a limp and thereafter used his left hand for writing. This blow did not diminish either his energy or his working capacity. Within a year he was back at his usual work, as industrious as before his illness and as capable in speech and writing as he had ever been. Four years later he published his monumental work, "The Brain from Ape to Man," which put him in the front rank of comparative anatomists and modern evolutionists.

In 1935, in spite of the advice of some of his friends to the contrary, he accepted the position of medical director of the Neurological Institute and held this position until the beginning of 1938, when the institute was merged with the Presbyterian Hospital. During these years he did an enormous amount of work in directing the policies and organization of the hospital and in caring for a large private practice. But he always found time to work in his laboratory and to continue the researches in comparative anatomy and morphology for which he was so well known. After he retired from the institute and from the medical school, he continued his anatomic work in the Museum of Natural History, in the department in which he had been a research associate for many years.

Recognition came early to Dr. Tilney and came to him deservedly all the rest of his life. He was secretary and treasurer of the Brooklyn Neurological Society in 1907 and 1908 and president in 1911 and 1912, president of the New York Neurological Society in 1917; secretary-treasurer of the American Neurological Association from 1917 to 1925, and its president in 1926. He was one of the founders of the Association for Research in Nervous and Mental Disease and its president in 1926; one of the editors of the ARCHIVES OF NEUROLOGY AND PSYCHIATRY from 1919 to 1934; chairman of the Committee on Research

and Publication of the Neurological Institute, and one of the editors of the *Bulletin of the Neurological Institute of New York*. He was vice president of the New York Academy of Medicine from 1931 to 1933, a trustee from 1935 until his death and a trustee of the Long Island College of Medicine from 1937. He was a member of many other medical and learned societies—the American Psychiatric Association;



FREDERICK TILNEY, M.D.
1875-1938

the American Philosophical Society; the New York Psychiatric Society; the Galton Society; the American Association of Anatomists; the Philadelphia Neurological Society; the Royal Society of Medicine, London, and the Verein für Psychiatrie und Neurologie, Vienna. In addition to his college and medical degrees, he was awarded the degree of PH.D. by Columbia University in 1912 and the honorary degree of Sc.D. in 1929.

Dr. Tilney contributed many papers to medical journals and wrote a number of monographs, beginning with one on the hypophysis. Perhaps his best known books are "The Brain from Ape to Man" and the classic textbook "The Form and Functions of the Central Nervous System," written with Dr. H. A. Riley.

Frederick Tilney worked very hard during his entire professional life, and whatever he essayed to do was done with unusual thoroughness.

He was greatly interested in the behavior and development of the normal and abnormal child and found time to give much thought to the studies of child development made under his direction. Although the demands on him were great, he made frequent visits to the Warwick Home for Delinquent Boys and directed the work of the Matheson Commission on Encephalitis.

He had a powerful physique and knew what it was to be physically fatigued, but mentally he was alert and untiring. He enjoyed the practice of his profession, and his patients were devoted to him. No amount of trouble was too much for him, and he was always doing unusual things for those who needed help. He never hesitated to take under his personal protection and guidance men and women who had physical ailments, such as the results of injuries at birth, and psychic disturbances, such as the neuroses. He was a physician in the real sense of the word and keenly felt his duties to his fellowmen who were in distress.

As a research worker he was honest and self critical, and it is easy to understand the close friendship that existed between Tilney and George S. Huntington. Both had marked physical and mental energy, unbounded enthusiasm, magnetic personality and brilliant intellect; both believed that morphology was the best means of interpreting the structure of the human body in its relation to function. The younger, Tilney, was greatly influenced by the older man, and until the end of his life he used the wax reconstruction method that had been favored by Dr. Huntington. From this work resulted some of the papers he published: "Brain Stem of Tarsius" (1927); "The Correlative Development of the Head and Brain in the Evolution of Intelligence" (1921); "The Pineal Gland" (1928); "The Structural Basis of Behavior" (1930); "Critical Phases in the Development of the Cerebral Cortex" (1932); "Comparative Ontogeny of the Cerebral Cortex in Four Mammals" (1932); "The Brain from Fish to Man" (1935); "The Development and Constituents of the Human Hypophysis" (1936); "The Hippocampus and Its Relation to the Corpus Callosum" (1938). These studies in morphology and comparative anatomy formed the basis for papers entitled: "The Brain of Prehistoric Man" (1927); and "The Brains of Some Early Tertiary Mammals of North America" (1931), and for many others on allied subjects. Aside from these articles and a number

of books, he published more than one hundred papers on clinical and other subjects.

Tilney had a combination of qualities which are rare. He was scrupulously honest in thought and action, had a degree of good nature and amiability which was sometimes almost a weakness and a keenness of intellect and a power of expression in speech and writing which are unusual. His character was so broad that he actually had little understanding for the petty things of life. He had great respect for the work of others, and the always ready expression of admiration for the work of his colleagues and friends was real and sincere.

That such a man should have been surrounded by many friends and admirers was natural. Those of us who were Tilney's friends will always regard him as highly for what he was as for what he accomplished; our admiration for his achievements will be always mingled with our affection for him as a man.

"His life was gentle, and the elements so mixed in him that Nature might stand up and say to all the world, 'This was a man!' "

CHARLES A. ELSBERG, M.D.

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